# Understanding Cortical Encephalitis

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[00:00:02] **Julia Lefelar:** Hello, everyone and welcome to a collaborative MOG cast with the Siegel Rare Neuroimmune Association titled, “Understanding Cortical Encephalitis and What Does It Have To Do with MOGAD?” Today we are speaking with Dr. Eoin Flanagan and Dr. Cristina Valencia Sanchez from Mayo Clinic. My name is Julia Lefelar, Executive Director and Co-Founder of The MOG Project, which is a US-based nonprofit organization devoted to raising awareness, advancing research, and providing support and advocacy for the MOGAD community in hopes of finding a cure.

[00:00:27] We'd like to thank our guests, the SRNA and the doctors, as well as the MOG Squad for their contributions to this MOGcast. So, I'm excited to introduce GG deFiebre of the SRNA as our special collaborator. So, GG, please go ahead and introduce yourself and tell us a little bit about the SRNA?

[00:01:00] **Dr. GG deFiebre:** Sure, thanks so much, Julia. My name is GG deFiebre. I'm Director of Research and Programs at the Siegel Rare Neuroimmune Association or SRNA. We're a nonprofit focused on support, education, and research of rare neuroimmune disorders, including MOG, and you can learn more about us on our website wearesrna.org. So, this MOGcast is being recorded and will be available on both our and the MOG Project's website, Facebook page, and YouTube channels. If you want to submit questions, you can do so on Facebook or in the webinar, as well, in the Q&A area.

[00:01:38] **Julia Lefelar:** Thank you. So, we're going to be answering community questions, time permitting. Any other questions that are unanswered are going to be answered in a follow-up MOG Blog. GG?

[00:01:51] **Dr. GG deFiebre:** Sure, so first, we'd like to introduce Dr. Eoin Flanagan from Mayo Clinic. Dr. Flanagan is a Professor of Neurology and Consultant in the Department of Neurology and Laboratory Medicine and Pathology at the Mayo Clinic. He did medical school at University College Dublin in Ireland in 2005 and later pursued neurology residency and neuroimmunology fellowship at Mayo Clinic. He received a master's degree in Clinical and Translational Science at Mayo Clinic and is principal investigator on an NIH R01 grant studying the epidemiology, pathology, radiologic features, and outcome of MOGAD.

[00:02:28] His clinical expertise and research is focused on MOGAD, Aquaporin-4 antibody positive neuromyelitis optica spectrum disorder, and transverse myelitis. He directs teaching courses at the American Academy of Neurology on autoimmune encephalitis and myelitis. He works in the Autoimmune and Multiple Sclerosis Neurology Clinics and the Neuroimmunology Laboratory at the Mayo Clinic. He also has an interest in paraneoplastic neurologic disorders, autoimmune encephalitis, and the epidemiology of MOGAD, NMOSD, and autoimmune encephalitis. Julia?

[00:03:01] **Julia Lefelar:** Well, thank you. So, I'm really excited to introduce Dr. Cristina Valencia Sanchez from Mayo Clinic. Dr. Sanchez is an Assistant Professor of Neurology at Mayo Clinic in Arizona. So, she's

originally from Spain, where she received her medical degree. She completed her neurology residency and Multiple Sclerosis fellowship at Mayo Clinic, Arizona followed by an autoimmune neurology fellowship at Mayo Clinic, Rochester. So, Dr. Valencia Sanchez is a Senior Associate Consultant at the Multiple Sclerosis and Autoimmune Neurology Division at Mayo Clinic, Arizona.

[00:03:39] Her clinical and research focus includes immune-mediated disorders that involve the central nervous system, such as MOG-IgG associated disease or MOGAD, neuromyelitis optica spectrum disorders, also known as NMOSD, multiple sclerosis, autoimmune encephalitis, and paraneoplastic neurological disorders. Dr. Valencia Sanchez is involved in ongoing clinical trials for autoimmune neurological conditions, including MOGAD. She's an editorial board member of the American Academy of Neurology Magazine Brain & Life in Spanish. So, GG, why don't you start us off?

[00:04:21] **Dr. GG deFiebre:** Sure. Thank you. So, first of all, kind of the main question of all of this is what is cerebral cortical encephalitis and what symptoms should patients look out for? Dr. Flanagan, do you mind answering this question?

[00:04:35] **Dr. Eoin Flanagan:** Sure, yeah. So, cerebral cortical encephalitis is an interesting syndrome, was first described by a Japanese group around 2017. And it was noticed that patients we generally think of demyelinating diseases involving the white matter of the brain. But this condition seemed to involve the cortex, which is some of what we call the gray matter, which is a little bit different, and it's on the outer surface of the brain. And what we tend to see patients present with is they present with seizures. Sometimes they have fever, headache; they can have weakness on one side. So, sometimes they can even present, like a stroke-like episode. So, these can be difficult to diagnose because when we do an MRI scan, we don't see changes in the white matter. Sometimes we just see changes within the cortex.

[00:05:41] A lot of times we'll do an MRI to look and then we'll see the swelling in the cortex and this bright signal within the gray matter on the surface of the brain. That's often just on one side of the brain. So, sometimes they call it unilateral cortical encephalitis. That's kind of a broad introduction. Then of course, the best way to diagnose it would be to do the MOG antibody test and confirm that the patient is MOG antibody positive. We also sometimes see some inflammation within the spinal fluid, as well as the MRI findings.

[00:05:54] **Julia Lefelar:** So, we know that cerebral cortical encephalitis is this new phenotype that's also been added to the 2023 International MOGAD panel's post-diagnostic criteria. Can you tell us a little bit about this decision, Dr. Flanagan?

[00:06:12] **Dr. Eoin Flanagan:** Yeah, sure. So, the diagnostic criteria was really important to give MOG antibody associated disease its own definition—that it's separate from MS and separate from neuromyelitis optica spectrum disorder. And it was also very important to have this category of disease because these patients sometimes people don't think about MOG antibody disease, and that can lead to a delay in diagnosis, and it's not until they have a second episode, maybe of optic neuritis that the diagnosis is made.

[00:06:42] So, having it written in stone in those diagnostic criteria is actually quite helpful so that physicians who read that article, because that's a commonly read article for physicians who want to learn about MOGAD, that this is a syndrome that they need to look out for.

[00:07:00] **Dr. GG deFiebre:** Great, thank you. And so, we've heard the term FLAMES associated with cortical encephalitis. What does this mean, Dr. Valencia Sanchez?

[00:07:10] **Dr. Cristina Valencia Sanchez:** Yeah, so, FLAMES is an acronym, and it stands for Unilateral cortical FLAIR-hyperintense lesions in Anti-MOG-associated Encephalitis with Seizures. And this is a term that was proposed in 2019 by a Canadian group led by Dr. Adrian Budhram. And basically, it's a term that tries to describe the clinical radiographic syndrome that we see with cerebral cortical encephalitis. In that paper, they reported one case of a patient that had a typical clinical presentation of cerebral cortical encephalitis with seizures, headache, fever.

[00:07:56] And who was found to have that typical abnormal signal in the cortex of the brain, which we call T2 FLAIR hyperintense because it looks bright when we do that specific MRI sequence. And then they reviewed the literature, and they found a little bit over 20 cases who had a similar presentation. So, they kind of created this term because it summarized very well that the presentation and the radiographic findings. So, it's really just another term to refer to cerebral cortical encephalitis.

[00:08:34] **Dr. GG deFiebre:** Thank you.

[00:08:37] **Julia Lefelar:** I think that what we want to do is look at a little bit of the incidence. How often is the MOG antibody detectable in people with this type of phenotype? Dr. Flanagan?

[00:08:50] **Dr. Eoin Flanagan:** Yeah, well, we think of this phenotype suggesting MOG, there's probably other things that can look like it. So, it's a little bit challenging to make the diagnosis and some of these patients, which we'll talk about later, end up being misdiagnosed. And actually, Cristina did a large series from Mayo Clinic group of patients. She led a study showing some of these changes. and we found it in about 6-7% of MOGAD patients. So, it can happen as their first episode, and it can happen later on.

[00:09:21] So, we think that this is a less common syndrome than the typical optic neuritis or myelitis, but still something that needs to be recognized because it's quite characteristic for MOG. So, I think the important thing for patients to remember is that sometimes they can have these symptoms, they can be one sided. And if they have those symptoms, that can be a symptom of a MOGAD attack and to let the physicians know, or for physicians to know, that they need to test for MOG antibodies when they see this kind of syndrome.

[00:09:57] **Dr. GG deFiebre:** And so, is this presentation more common in children or adults or does it kind of happen equally distributed between these groups? Dr. Valencia Sanchez?

[00:10:09] **Dr. Cristina Valencia Sanchez:** So, cerebral cortical encephalitis may happen both in children and in adults. When we looked at the Mayo Clinic patients with MOGAD who had a presentation consistent with cerebral cortical encephalitis, we found the youngest patient was two years old and the older patient was 47 years old. The median age was 14 years old. And then of the 19 patients that we had, there were 12 of them who had childhood onset and seven of them who had adult onset.

[00:10:46] So, it seems to be a little bit more frequent in children. And in terms of what that represents compared to the total cohort for children, it was about 13% cases of cerebral cortical encephalitis in our cohort and for adults, it was about 4% of our total MOGAD cohort.

[00:11:11] **Dr. Eoin Flanagan:** And maybe I could jump in just one thing just to say that these cerebral cortical encephalitis episodes, we sometimes think of MOG or people say MOG is mild disease or [recovery]. But these patients can be really sick and sometimes they're in hospital, they can be in the ICU. They can have what we call status epilepticus, which is just constant seizures.

[00:11:29] They may need ventilation, breathing tubes, they can have high intracranial pressure. So, it's really important that doctors recognize these and know to treat them aggressively because MOG-antibody-associated disease can recover quite well, but these patients can be really, really sick. So, that's another thing I thought to add to.

[00:11:50] **Julia Lefelar:** That's really good information. So, to the best of your knowledge is this particular presentation more likely to be associated with the first CNS presentation or is it more seen as a relapsing presentation?

[00:12:07] **Dr. Cristina Valencia Sanchez:** So, it can happen in both. It may happen in patients as a first presentation, but it can also happen in patients who have a prior history of MOGAD attacks, for example, with optic neuritis or myelitis. And when we analyzed those 19 patients in our cohort, what we found is that 68% of them, the cerebral cortical encephalitis was their first presentation and then 32% had prior MOGAD attacks. Another thing that I think it's important to mention is that in the patients with cerebral cortical encephalitis, they could actually have, in addition to the cerebral cortical encephalitis, they could have additional MOGAD phenotypes that may occur within one month.

[00:12:58] So, for example, a patient could present with cerebral cortical encephalitis and optic neuritis or cerebral cortical encephalitis and myelitis. And we found that in about 63% of our patients who had other MOGAD phenotypes within one month of the onset of the cerebral cortical encephalitis presentation, which you know, we typically consider that one month timeline as being the same attack in general. And then another thing that I think it's important to mention is that in our cohort, we also had three patients who had recurrence of the cerebral cortical encephalitis. So, they had new relapses with cerebral cortical encephalitis later in life.

[00:13:45] **Dr. GG deFiebre:** Thank you for that. And so, if someone is suspected that they have MOGAD associated encephalitis, what are some common tests that need to be performed to really solidify that diagnosis and exclude other diagnoses like an MDA receptor or viral encephalitis? Dr. Flanagan?

[00:14:09] **Dr. Eoin Flanagan:** Yeah, I think we touched on this a little bit earlier, but I think the major test that we often do is an MRI of the head. The one thing we might touch on later, too, is that the MOG and Cristina was getting at this, that the MOG is very dynamic, it changes a lot very quickly. So, sometimes even the initial MRI can be normal, and then you do an MRI a week later, and you'll see the cerebral cortical encephalitis. So, it changes quite a lot. So, it's important if a patient is getting worse or that you repeat the MRI if you're not sure of the diagnosis. The other test that we do of course test the MOG antibody usually in blood, but we can also do spinal fluid testing of MOG antibodies and that is often positive also.

[00:14:52] And then do a spinal fluid analysis and look for other infections because infections can cause similar changes in the brain on MRI and similar symptoms. And when the patient has a fever, we always worry about infection. But I think it's also important not to anchor on infection because some of these cases then get misdiagnosed as an infectious cause. So, it's important to test for different types of infections. And Cristina might get into more later, but sometimes patients can have NMDA receptor antibodies and MOG antibodies. So, it's good to test for those NMDA receptor antibodies, too, because that might change your treatment approach a bit.

[00:15:31] **Julia Lefelar:** In this diagnostic process, what if the titer is it one of those low positives? How do you handle that?

[00:15:41] **Dr. Eoin Flanagan:** That one was for me I think so. So, I'll just touch on that. One of the major problems with the MOG antibody test is that it's a little bit sticky. So, that means that people who don't have

  

MOG antibody disease who have MS may have a low-titer. What I will say with the cerebral cortical encephalitis is most of the time the titer is quite high. So, usually it's quite high, particularly early on with the disease, but we always have to make sure that we know we're dealing with MOG.

[00:16:09] So, that's where you bring out your diagnostic criteria, and you look through the syndrome. Does it fit with the cerebral cortical encephalitis? Are there other diagnoses that are more likely? You know, if you have oligoclonal bands in your spinal fluid, if you have other changes within your spinal cord, there can be a suggestion of MS, but really the cerebral cortical encephalitis syndrome is quite unique. So, if it has a positive MOG antibody, it looks like that, it's probably going to be MOGAD, I would say.

[00:16:37] **Dr. GG deFiebre:** Thank you. And so, once someone is diagnosed with cortical encephalitis, what is the best treatment for those who have this diagnosis? We'd love to hear opinions based on both of your perspectives. But Dr. Valencia Sanchez, do you mind starting?

[00:16:53] **Dr. Cristina Valencia Sanchez:** So, in most of the diseases with cerebral cortical encephalitis that have been reported in the literature and also what we saw in our patients is that most of them had a good response to treatment with IV steroids. Most of them had a clinical improvement with the IV steroids. And also, most of them had resolution of the abnormalities that we see in MRI after the treatment with the steroids.

[00:17:23] So, that is always our first line therapy, we typically do five days of IV methylprednisolone 1000 mg daily. So, that is the first line. In cases who have attacks on that refractory to the IV steroids or who have a very severe presentation, other treatments to consider in an acute setting are plasma exchange and IVIG as well.

[00:17:52] **Dr. Eoin Flanagan:** And there have been some – Oh, go ahead Julia.

[00:17:54] **Julia Lefelar:** I was going to say, go ahead, Dr. Flanagan.

[00:17:56] **Dr. Eoin Flanagan:** Yeah, there have been some reports in patients who are really, really sick. Other treatments have been used as one called Tocilizumab that targets an IL-6 treatment, or even some patients with cerebral cortical encephalitis or other types of severe encephalitis, children can have really what we call fulminant or very severe presentations where they get the pressure goes up in the brain and it can be really life threatening. And in some of those times, you have to involve neurosurgery and you have to do procedures to try and reduce the pressure.

[00:18:27] So, sometimes that can happen in a very acute setting. So, that's another thing. And then I think the other thing to mention would be seizures are common. So, we'll often treat seizures with anti-seizure medications in that situation. And then the patients often need a lot of supportive treatment. So, they'll be in the hospital and need some rehabilitation after they recover, as they recover from the episode.

[00:18:52] **Julia Lefelar:** Thank you, that's a great answer. So, this might be a loaded question, but we want to hear from both of you and just your opinion, then. So, why is this presentation often misdiagnosed for something different? And sometimes we've heard it results in unnecessary brain biopsy in about 47% of patients. Dr. Sanchez, do you want to start?

[00:19:22] **Dr. Cristina Valencia Sanchez:** Well, first of all, I wanted to clarify in the 47, so in our cohort we did find that 47% of the patients were initially misdiagnosed, but not all of them ended up having a brain biopsy. Four of the patients in our group, in our cohort, had a brain biopsy. And one of the reasons why this is often misdiagnosed is because it is one of the less recognized MOGAD phenotypes. Although, hopefully, now that more and more cases are reported. that we are increasing the awareness of this condition among clinicians.

[00:20:04] And the other thing is that the clinic representation can resemble the clinical presentation of other conditions, such as infectious meningitis or meningoencephalitis. So, the most common misdiagnosis is actually an infectious encephalitis or a meningitis. So, what we found is that most of our patients were actually initially treated with antibiotics, antivirals because they were suspected to have an infection because they presented with headache, with fever; they were found to have elevated white blood cells in the spinal fluid.

[00:20:43] So, the first thought was that it could be an infectious process. And sometimes the abnormalities that we see in the MRI with cerebral cortical encephalitis may be subtle. So, sometimes those abnormalities could be missed. And then in terms of the patients who had the brain biopsies, most of them, the thought that the physicians had at that time and the reason why they ended up having a brain biopsy is because sometimes they thought that they could potentially have vasculitis, which is an inflammatory disorder that affects the central nervous system that may also percent with headaches, with seizures.

[00:21:28] And it is something that may also cause the strokes. And as we said before, patients with cerebral cortical encephalitis may present with one weakness of one side or speech difficulties. So, sometimes people may think that those are stroke symptoms. So, those were the reasons why those patients ended up having a biopsy. So, we really want to increase awareness of these MOGAD phenotype because it's very easy to check MOG-IgG in the blood and avoid unnecessary testing and make sure that the patients get treatment with immunotherapy early to improve their outcomes and their prognosis.

[00:22:12] **Dr. Eoin Flanagan:** Cristina covered that really great, comprehensively. I'll just mention one thing is that sometimes in children, when they present with these syndromes there's a fear to giving steroids because they think it's an infection, but probably five days of steroids, even if it was an infection is not going to cause too much harm. So, it does take a while for the MOG antibody to come back.

[00:22:35] So, if there's ever a suspicion the earlier the steroids is going to be the better to prevent this going into a very severe episode. So, I think patients and physicians need to really push for that early steroid treatment to get in quickly. And then hopefully, that can kind of stop it in its tracks and get things moving in the right direction quicker.

[00:22:57] **Dr. GG deFiebre:** Thank you. And so, what are some other forms of autoimmune encephalitis that occur in MOGAD? And what are the differences between these and cortical encephalitis? Dr. Flanagan?

[00:23:11] **Dr. Eoin Flanagan:** Yes, great question. So, I suppose the main other type is a syndrome called acute disseminated encephalomyelitis, which is kind of a bit of a mouthful. But it means, the terms mean acute inflammation within the brain and the spinal cord that's in multiple locations. And usually, those locations are in the white matter that we talked about earlier. The brain has white matter and gray matter, and the gray matter on the surface is called the cortex. And usually those syndromes, at least on the MRI scan don't seem to show as many changes in the cortex.

[00:23:45] So, when there are changes in the cortex only, that's when we think about the cerebral cortical encephalitis. When we've got lots of changes within the white matter and the spinal cord, we think about this syndrome called acute disseminated encephalomyelitis. And they're overall pretty similar, both are a bit more common in children, and the acute disseminated encephalomyelitis, or what we term "ADEM," does often have or has to have really confusion associated with it or alternation in consciousness, but doesn't tend to have probably as frequent seizures as a manifestation like the cerebral cortical encephalitis.

[00:24:17] But patients with MOGAD can also get inflammation in other regions like in the brain stem or in the cerebellum that controls your balance. So, people can develop double vision, they can develop imbalance

  

from inflammation within the brain that would come under the spectrum of encephalitis. So, and I think in children, as we mentioned, sometimes that NMDA receptor antibody can also be present. So, you can have a combination of this NMDA receptor encephalitis that can have psychiatric symptoms, memory loss, sometimes difficulty with breathing, abnormal movements in the face.

[00:25:03] So, sometimes you can get that overlap syndrome. And I think particularly in children, there's a whole variety of different encephalitis types that you can have. So, if you have encephalitis in a child, really, unless there's a definite other answer right away, you should be checking for MOG antibodies because it's a broad set of symptoms and signs that patients can have in MRI findings. So, it can be difficult to categorize them all together. So, it's important just to check for the MOG antibodies in that situation.

[00:25:33] **Julia Lefelar:** Thank you. That's all great information. So, looking at the incidence of these other forms of encephalitis in comparison with the cortical encephalitis, can you speak to that? And Dr. Sanchez, we ask you?

[00:25:50] **Dr. Cristina Valencia Sanchez:** Yeah, so, of the other forms of encephalitis that Dr. Flanagan just mentioned, the most common one is actually ADEM, the acute disseminated encephalomyelitis, which is actually the most common initial presentation of MOGAD in children. So, up to 60% of children with MOGAD have a presentation with acute disseminated encephalomyelitis. This may also occur in adults, although it's not as frequent as in children. The incidence of other types of encephalitis is more rare.

[00:26:26] So, as we mentioned before, with the cerebral cortical encephalitis, it was about 7% of our cohort. And in terms of that overlap syndrome that occurs between MOGAD and NMDA autoimmune encephalitis, we also looked into this at Mayo in our cohort of MOGAD patients and we found that about 4% of patients with MOGAD also had NMDA receptor antibodies and [autoimmune] encephalitis as a result of that.

[00:27:05] **Dr. GG deFiebre:** Great, thank you. And so, what is the prognosis for all of these forms of encephalitis in MOGAD? What are the potential long-term effects in both adults and children? Dr. Flanagan?

[00:04:35] **Dr. Eoin Flanagan:** Yeah. Well, I think the overall outcomes are good in that people tend to recover, but they can be, as I said earlier, they can be quite severe. So, it's really important that they're treated aggressively. So, they might require time in the ICU, early steroid treatment. You know, the treatments Dr. Valencia Sanchez mentioned earlier—plasma exchange, IVIG, potentially Tocilizumab involving neurosurgery if it gets very severe or increased pressure within the brain.

[00:27:47] So, but actually, then afterwards patients tend to recover. And one thing we've recognized is that, clinically, patients tend to make a good recovery. It may take many weeks or months, but then they can recover back. But of course, then they can be at risk of developing further episodes down the line, but they do tend to make a good recovery. And one of the things with MOG-antibody-associated disease also is that the lesions in the brain tend to resolve. So, it's a bit different to multiple sclerosis, which means "multiple scars," where MS the lesions always leave a scar. With MOGAD, the lesions tend to resolve, but they can leave some long-lasting damage.

[00:28:25] And I think we need to delve into a bit deeper about some of the cognitive testing and things like that because there are probably some sequelae after these episodes and some damage that maybe we can't measure in looking at people. But patients will tell us that they struggle with day-to-day activities. They may have difficulties with attention and other aspects of fatigue. So, there can be some long-lasting symptoms even though patients tend to recover well, they get out of the hospital, they can walk, they can see, but they may have some cognitive issues and ongoing symptoms after that.

[00:29:00] **Dr. GG deFiebre:** Anything to add, Dr. Valencia Sanchez?

[00:29:03] **Dr. Cristina Valencia Sanchez:** So, I completely agree with what Dr. Flanagan said, and I think that it's important to do more research particularly in the cognitive long-term [inaudible] symptoms for patients with MOGAD because some of the measures that we typically use rely very heavily on what is the motor function, what is the vision. But we don't have as much data in terms of cognitive impairment in the long term. So, I think that there is an area that would definitely be good to do some more research in.

[00:29:44] And I also wanted to mention that for that small group of patients who have that overlap with MOGAD and NMDA encephalitis, those patients tend to recover better from the MOGAD manifestations, the visual and the motor symptoms that may come more from the MOGAD. But from the standpoint of the NMDA encephalitis, they frequently have cognitive symptoms in the long term. Sometimes up to 70% of the patients have some residual neurocognitive symptoms.

[00:30:29] **Julia Lefelar:** Thank you for that. Can autoimmune encephalitis occur in a patient at any time in their life or MOGAD course? Even after having bouts of optic neuritis or transverse myelitis? The reason I ask this is we have at least one person we know of who suffered from an encephalitis attack after years of being diagnosed with MOG-positive NMOSD. We'd love your opinion, both of your opinion on this. Dr. Flanagan, do you want to start?

[00:31:00] **Dr. Eoin Flanagan:** Sure, yeah, I think there is a potential for inflammation within the brain at any time. What I'll say is that the most common type of relapse is still the optic neuritis. So, that's the one we look out for most and maybe spinal cord next. But the brain inflammation can occur at other times. So, we have to always be mindful of that. And if a patient, some patients can have many years between attacks, so they can go 10 years without attacks, and then suddenly they can get inflammation.

[00:31:29] And we don't really have a good understanding of, one, why does it happen in certain locations? And one why does it come at this time rather than a year earlier, or five years subsequent? So, it's a little bit difficult for us to predict. But I think we know the areas that the MOG affects, and it affects the central nervous system, the optic nerve, the brain, and the spinal cord. So, they're the areas we need to focus on. And if a patient has any symptoms in any of those regions, we should take it very seriously and look at that.

[00:31:57] And as I said, sometimes there can be some confusion because of that delay in the imaging because MOG changes a lot, and sometimes the initial imaging doesn't show very much or doesn't show it. And then in follow-up, you repeat the imaging, and you see 10 new lesions. So, it's always important if you're not seeing something right away to reassess within a few weeks and maybe repeat the MRI, and then you may see the changes become more obvious later on.

[00:32:22] **Julia Lefelar:** That's a really good point. I think that didn't happen in one person's case, so surely a lesson learned for all physicians who are looking at this. Dr. Sanchez, I'd love to have you follow up and get your opinion on that.

[00:32:39] **Dr. Cristina Valencia Sanchez:** Yeah, I agree. I think there is potential for encephalitis to occur at any time, and we did in this group of patients with cerebral cortical encephalitis that we studied. Some of them had a prior attack of optic neuritis or myelitis or ADEM years before they were diagnosed with cerebral cortical encephalitis. So, yeah, that is something that could potentially occur.

[00:33:11] **Julia Lefelar:** Thank you. To follow up, I guess it sounds like it's something that needs further study, correct? How can the MOGAD community help in that manner? Dr. Sanchez, I'll start with you.

  

[00:33:25] **Dr. Cristina Valencia Sanchez:** Yeah, so, I do think that we are still learning a lot about MOGAD, and there is some research going on. So, yes, I agree that it would be good to have more long-term data, patients who have had the disease for years and to see what happens with the relapses, when do they have relapses? Right now, for example, we don't have a good guideline as to how long to keep patients on preventive therapy. How do you predict whether, if we stop the therapy, whether they are going to have any relapses years later? So, yes, those are definitely things that we need to work on.

[00:34:17] **Dr. Eoin Flanagan:** I can make a quick comment. We're so lucky that the many of the MOGAD patients out there come, each different patient we see, we learn something from and some of those patients sign up to be involved in research. That can really help us learn more about the disease.

[00:34:37] We're looking at different types of biomarkers, different tests and blood, different types of MRI sequences. So, every patient that we see tells us a story, and then we use that information to try and learn more about the disease because we're in the early stages of MOGAD. You know, it was only really first discovered in 2007. The tests became available in the USA maybe in 2017 or so. So, really this is a new disease.

[00:35:01] So, we're learning every day, and we really appreciate all the patients who are willing to participate, who come to see us, and we learn so much from them every day. So, all the stories that we tell and Cristina's excellent article on the cerebral cortical encephalitis came from those patients telling us their stories and us being able to look at their information.

[00:35:21] **Julia Lefelar:** Yeah, well, so many are happy to do that. And we're just thrilled that we can work closely to bridge that gap between patients and places like the Mayo Clinic who do just such great research. Thank you, Dr. Flanagan, and Dr. Sanchez. So, we have this community question, and I'll try to see if I can read it. So, the person writes in, and they said, "Our daughter was originally diagnosed as ADEM with her first MOG episode, but her doctor recently said that it was more likely cerebral cortical encephalitis.

[00:35:57] Is there any long-term impact differences we need to be concerned about or differences in future relapses? She is currently receiving IVIG every four weeks." And I know you touched on this a little bit, but I wondered if you could address this, and I guess Dr. Sanchez, do you want to start?

[00:36:18] **Dr. Cristina Valencia Sanchez:** Sure. So, I would say that when we looked into our patients with cerebral cortical encephalitis, we actually found that some of them also have lesions in other areas of the brain and actually that these lesions looked like the typical lesions that we see with ADEM. In addition to that, they also had the abnormalities in the cortex that we see with cerebral cortical encephalitis. So, I can see how perhaps that this particular patient, there was that change in the diagnosis. But in terms of the long term...

[00:37:00] So, as we discussed before, usually after the acute treatment with the steroids, a lot of the patients get better. And in terms of preventing future relapses, I think that the treatment with IVIG every four weeks is appropriate. There are different therapies that have been tried as preventive treatments for MOGAD, but there was a study that was led by Dr. Chen at the Mayo in Rochester showed that IVIG seems to be associated with the less chances of having relapses. So, I do think that would be a good treatment.

[00:37:46] **Dr. Eoin Flanagan:** And then I'll just, I might make a quick comment on that just to mention, not specific to this case, but for people out there who may have a new diagnosis of MOGAD and have had two or more attacks, there are clinical trials. Now, I know Julia mentioned that their Mayo Clinic is involved in the many centers in the USA and around the world. So, if you do have MOGAD, you develop that second attack, you've not been on any treatment, do consider being involved in the trials because that's the only way we can prove a medication works.

[00:38:18] So, at the moment, we have no proven medication. We think that IVIG and some of these treatments work well, we have to do our best with what evidence we have available. But it's really important that we can complete these clinical trials to really find some proven treatment and they involve some people going in the placebo arm and there's a way that we can really prove it scientifically so that we can get FDA-approved medications for patients.

[00:38:41] So, I think we're hopeful that we can enroll patients in these trials and really bring successful treatments for patients that can be FDA approved. Because many times we struggle with insurance, getting these medications approved for patients. And it's a real challenge. So, if we can fill up these trials and really prove a medication works, that will be really helpful for all of the people with MOGAD out there.

[00:39:09] **Dr. GG deFiebre:** And so, earlier we talked about how in cortical encephalitis, the gray matter is affected. Is there any theorized reason why that might be the case in this particular presentation, or are we still kind of learning about that? Dr. Flanagan?

[00:39:27] **Dr. Eoin Flanagan:** Yeah, I can have a go at that. Yeah, it's a hard question. I don't think we fully know, you know, there's other parts of the brain that have gray matter that are deeper in the brain called the deep gray matter, something called the thalamus and the basal ganglia. And they also tend to be involved with MOGAD, and the myelin is the insulation in the nerves and there is insulation—that insulation is also in the gray matter. It's mostly in the white matter, but it's also in the gray matter. There are some people that have a suggestion that maybe it's an outside-in process.

[00:39:57] So, maybe you get inflammation along what we call the covering of the brain called the meninges, which is the outer covering of the brain. And that spreads to the cortex and maybe there's something coming from outside in, but I don't think we really fully know, and then some patients have ADEM, then they have cortical encephalitis. Some have both. So, it's very much a spectrum and it's complicated. So, it's difficult for us to be sure of the exact reasons.

[00:40:24] **Dr. GG deFiebre:** Anything to add, Dr. Valencia Sanchez?

[00:40:27] **Dr. Cristina Valencia Sanchez:** No, I agree with Dr. Flanagan.

[00:40:36] **Julia Lefelar:** We actually have another question that came up, and do you think that this cortical encephalitis would lead to a change in preventative treatments in the future? And this is an opinion I'd love to hear from both of you. And so, Dr. Sanchez, do you want to start?

[00:40:58] **Dr. Cristina Valencia Sanchez:** Whether cortical encephalitis will lead to change of preventive treatments?

[00:41:03] **Julia Lefelar:** Yes.

[00:41:04] **Dr. Cristina Valencia Sanchez:** So, I do think that really the treatment for cerebral cortical encephalitis is the same that we would do for other MOGAD attacks, both in the acute setting and as a preventive because it's really, as we were saying, a spectrum of manifestations that we see in patients with MOGAD, and we still do not know why patients may present with one or other phenotype. But I do think that in terms of preventive treatments, it would probably be similar for encephalitis and for other MOGAD presentations.

[00:41:46] **Dr. Eoin Flanagan:** I agree completely with Cristina, yeah.

[00:41:49] **Dr. GG deFiebre:** Okay, thank you. And so, we actually just had a question that says, "How important is the distinction between ADEM and cortical encephalitis from a treatment point of view?" Dr. Valencia Sanchez?

[00:42:06] **Dr. Cristina Valencia Sanchez:** Yes, I think it's so similar to what we just discussed. I do think that from a treatment standpoint, regardless of the phenotype that the patients present with, we are always going to do the steroids. If refractory, we are going to do the plasma exchange, IVIG, consider Tocilizumab in those kind of more fulminant cases. And then the symptomatic management, perhaps one of the things is that cortical encephalitis tends to present with more seizures. So, these are patients who will likely also need anti-seizure treatment. And then if there are any signs of increased intracranial pressure, when there is a lot of inflammation in the brain, then measures to treat that as well.

[00:43:05] **Dr. GG deFiebre:** Thank you. And so, Dr. Flanagan, can you tell us a little bit about the recent study on diagnostic utility of MOG antibody testing in cerebrospinal fluid?

[00:43:16] **Dr. Eoin Flanagan:** Sure, yeah. This is an interesting area and a kind of hot topic at the moment. So, most of the time when we test patients for the MOG antibody, we do it with their blood. So, it's easier to do a blood test than to do a lumbar puncture or a spinal tap. But there are certain scenarios where if the syndrome, the way the patient is presenting looks very like MOG and the blood test is negative for whatever reason. And sometimes if they've had some preceding treatment that could affect it, then we can look at the spinal fluid.

[00:43:09] And sometimes we can find patients who only have the antibody in the spinal fluid. We have to be careful because, like I said earlier, the MOG antibody is a little bit sticky. So, we have to always be careful. But also in some patients, it can be useful if the MOG antibody is low in the blood. If you find it in the spinal fluid also, it makes it more likely it's relevant and it's not a false positive. So, there are some uses for the spinal fluid. It's probably not quite as useful as the blood for the testing of MOG, but it looks like overall that it might be a reasonably good test.

[00:44:23] It looks like that the live cell-based assay. So, we have live and killed cell-based assays that we use, and the live cell-based assay really more recapitulates what happens in real life. So, we found that looks to be a little bit better, but it's something we're kind of doing research on right now. It's not widely available. So, we're hoping that that might be something to make available in the future so that we can make sure we don't miss any cases of MOGAD, but Cristina can comment, too, who was also involved in the study, yeah.

[00:44:53] **Julia Lefelar:** Yes, we would like to hear.

[00:44:55] **Dr. Cristina Valencia Sanchez:** No, I completely agree with you Dr. Flanagan.

[00:45:00] **Julia Lefelar:** Thank you. Well, this has been an incredible discussion, and we always end our MOG casts really asking both of you about your most recent work, and I know that we just talked about this study that just came out. But I'd still like to hear from both of you things you'd like to share with the community, brag about, whatever it is. So, Dr. Flanagan, we'll start with you.

[00:45:29] **Dr. Eoin Flanagan:** Yeah, I'll just mention one thing. We touched on it a little bit earlier, but we do have a study that will be coming out soon showing that MOG changes a lot over a short period of time within those attacks. So, sometimes with MS and with neuromyelitis optica and other conditions, we don't see much change if we do a repeat image a week or a few weeks after an attack. But in the MOG, sometimes it will go from one lesion to 10 lesions within a couple of weeks.

[00:45:56] Or sometimes you might have 10 lesions and then a few lesions go away within a few weeks. So, it's very dynamic, and it changes a lot. So, if there's ever any suspicion of worsening or not sure about the diagnosis, the initial MRI was normal, don't be afraid to repeat that MRI down the line, and I think we can learn about this. Why is MOG changing so much? Why are those lesions resolving, for example, rather than in MS, where they leave scars?

[00:46:21] And I think some of that is why MOG patients tend to do better overall in the long term is because some of these lesions resolve. So, I think if we could learn more about that, it would help us understand many of the demyelinating diseases. So, that's kind of one area we're interested in—how lesions change, how they resolve, and how the MOG changes so rapidly in short periods of time.

[00:46:47] **Julia Lefelar:** That's great. Dr. Sanchez, I'd love to hear from you.

[00:46:52] **Dr. Cristina Valencia Sanchez:** Yeah, so, we do collaborate here at Mayo in Arizona with all the studies that Dr. Flanagan is leading at the Mayo in Rochester. So, perhaps I can mention that we are also working on another study looking at the patients with MOGAD who have elevated intracranial pressure, which is an observation that has been made in several case reports that when these patients have a lumbar puncture, some of them have very high pressures, and sometimes this is one of the things that may confuse physicians and they may not think about MOGAD.

[00:47:35] So, this is something that has been observed, it seems to be more often in patients who have several cortical encephalitis and patients who have ADEM. So, that is something that will probably be available soon. And I wanted to mention as well that we are also participating in the clinical trials at Mayo Rochester and at Mayo Arizona and Mayo in Jacksonville. I mean, it's really a very exciting time for MOGAD because we are doing, we have the first two clinical trials, and we are all hoping that this will lead to have FDA-approved therapies soon because that is something that we all struggle with.

[00:48:26] Sometimes it's hard to get treatments for our patients particularly for the preventive treatments when there is nothing FDA approved, that is something that insurances like to use to deny treatments. So, I think that is really, really important—the work on the clinical trials. And we are actively including patients for the CosMOG trial, which is with an agent that is called [Rozanolixizumab], which works similarly to IVIG.

[00:48:58] And then there is another trial that is called Meteoroid with an agent called Satralizumab, which is actually a medication that is currently approved to treat neuromyelitis optica with Aquaporin-4 antibodies. So, this clinical trial will determine whether this is something that we could also use for MOGAD.

[00:49:20] **Dr. Eoin Flanagan:** And I, oh, sorry to interrupt. I'll just echo Cristina's or Dr. Valencia Sanchez thoughts there too. I think there's a lot of hope out there for our MOG patients. There's a lot of people interested in MOG. There's lots of research going on. We're trying to bring treatments forward. So, stick with us and we'll get there, and we'll have lots of treatments in the future. But we appreciate everybody trying to be involved in the research, people getting involved in the trials because it's going to be so important to bring us forward where we have really strong treatments, and we can really help our MOGAD patients.

[00:49:55] **Dr. GG deFiebre:** Thank you. Yes, it's a very exciting time with treatments on the horizon. So, we got another question about [fulminant] cortical involvement cases. Are there any guidelines on offering preventive elective craniectomy to prevent pressure changes?

[00:50:16] **Dr. Eoin Flanagan:** I can jump in there. Yeah, because that was an interesting point. Yes, so, I do think there are patients where they really deteriorate very rapidly, and I think you have to treat them as

  

aggressively as you can. And that was part of what I mentioned about involving neurosurgery and sometimes to relieve the pressure, you can take off the skull temporarily, that's done sometimes with very large strokes, for example, and can be successful. And it has also been successful in some patients with MOGAD.

[00:50:43] So, I think for these patients who have this very severe attack, high pressures where there's a risk of too much pressure in the brain causing severe damage and even death. It's really important that we do everything we can because the patients can then recover if we can get them to treatment. But we just sometimes need time for that pressure to go down. So, certainly taking off the skull if that needs to be done, should be done. And involving neurosurgery early for these patients who are really deteriorating is so important.

[00:51:16] **Julia Lefelar:** Thank you, Doctor Flanagan. You know, at the 11th hour we've had a few more community questions that we'd like to throw at you all, and there's probably too many to answer, but we'll see. So, one is that one person asked, "My daughter is on Rituximab for about two years and has been off it now for over a year, yet her IgGs continue to decline. The question is, is this typical? And how long does it typically take for her IgGs to start increasing?"

[00:51:54] **Dr. Eoin Flanagan:** I don't mind. I'm happy to, you want me to go Cristina? I'll jump in, yeah. So, I think the Rituximab medication targets your B cells. So, we all have B and T cells in our immune system, and the B cells make your antibodies. So, the Rituximab reduces all your B cells and then you don't make enough of these antibodies, and your antibody level can go down. So, the Rituximab does have a long-lasting effect. So, it can affect your immune system for even a year, a year, and a half after.

[00:52:27] So, usually, eventually, those IgG levels will come back up, but sometimes it can take a while, even a few years to come back up. One of the potential treatments was something that Dr. Valencia Sanchez mentioned earlier, was that IVIG treatment. So, if it's too low and somebody's having infections temporarily, they could receive IVIG treatment to boost that IgG up, and that can help prevent against infections for that time period while you're waiting for that IgG to come up. So, that could be something to discuss with the physician too.

[00:53:01] **Julia Lefelar:** Dr. Sanchez, go ahead GG.

[00:53:06] **Dr. GG deFiebre:** Anything to add to that?

[00:53:08] **Dr. Cristina Valencia Sanchez:** Yeah, I completely agree, and I would say that I've had a number of patients who I treated with Rituximab. And then I was surprised to see how long actually the Rituximab had an effect on depleting the B cells. So, yes, that is something that could happen and that really needs to be monitored, yeah.

[00:53:34] **Dr. GG deFiebre:** And then, we got asked another question about if there is anxiety attacks and mood swings in ADEM? Dr. Valencia Sanchez?

[00:53:46] **Dr. Cristina Valencia Sanchez:** So, anxiety and mood swings are things that may happen in MOGAD, but also in a variety of conditions. So, it is so frequent in the population that it's hard to demonstrate exactly whether there is something that is related to those regulations, and we see that not only in patients with ADEM but also with other phenotypes but, yes, that anxiety is definitely a common presentation and mood disorders, yeah.

[00:54:26] **Dr. Eoin Flanagan:** And I'll just mention sometimes the steroids can make those a bit worse or trigger them. So, sometimes we have to bring people down on steroids a little bit more quickly to try and

  

reduce some of those irritability, mood changes, even psychosis where people can get very confused and psychiatric issues related to those treatments.

[00:54:48] **Julia Lefelar:** Okay, thank you. One more question asks, "If your MOG antibody goes negative after a year and a half of the IVIG therapy, would you typically go off or taper down the IVIG at that point after a year of those antibodies being negative?" Dr. Flanagan, would you?

[00:55:14] **Dr. Eoin Flanagan:** Yeah, I can comment on that. So, yes, what we know is that the MOG antibody is highest when you first have your episode, and some people will go negative. I think we mostly base our decisions based on how the clinical situation has been. So, because some people, even after the antibody goes negative, it might just be below the cut off and still they can have attacks. So, we more base our decisions around how they are doing clinically, how many attacks they have had.

[00:55:41] But the people who do go negative tend to have a lower risk of future relapse but not zero. So, sometimes the antibody will come back up a little bit over the threshold and they can have relapses or even sometimes they can have relapses when it's negative. So, we tend to base it more on how many clinical attacks they've had and how they have been over time.

[00:56:02] **Julia Lefelar:** Thank you. Dr. Sanchez, do you concur? Is there anything you want to add?

[00:56:06] **Dr. Cristina Valencia Sanchez:** I do. I completely agree, and I think that that is another area for research trying to find other biomarkers that help us a little bit better to predict or reduce the risk for relapses given that the antibody titers may help us a little bit, but they are not completely accurate. So, in the sense that, you know, patients who are positive could be a relapse and patients who are negative could have relapses. So, it would be good to actually to have other biomarkers that help us a little bit more to make those decisions.

[00:56:40] **Dr. GG deFiebre:** Thank you. And we have one last question, which is, "Is there a cure in sight for ADEM?" Dr. Valencia Sanchez?

[00:56:53] **Dr. Cristina Valencia Sanchez:** Nothing that we have here in sight right now. But I do think that we do have a lot of research going on, on a lot of treatments that seem to be very promising. So, that at least we could put things early, improve the prognosis, and hopefully put the patients on preventative treatments that will avoid relapses in the future.

[00:57:31] **Julia Lefelar:** Dr. Flanagan, do you have anything to say with that?

[00:57:34] **Dr. Eoin Flanagan:** I agree completely with Dr. Valencia Sanchez. We're always looking for a cure. I think some of these medications we're hopeful will really bring us to being able to manage the disease very well and prevent future attacks. So, we're very hopeful again for the future, yeah.

[00:57:53] **Julia Lefelar:** Well, thank you for that. And it's been a great hour with you two, and lots of questions. It is a hot topic, and we're very thankful for your time. So, again, we'd like to thank the both of you and your commitment, especially to the MOGAD community. So, everybody, please look out for our follow-up MOG blog and any questions that maybe people add after this, we will put that in the MOG blog, but mostly we'll be talking about the impressions from the MOG cast today. So, thanks everybody. It's a great discussion, and everybody have a great rest of the afternoon.

[00:58:32] **Dr. Eoin Flanagan:** Thanks Julia and GG to the SRNA and The MOG Project for such great advocacy. And this MOG Awareness Month has been really great to shed a light on the disease. So, thanks so much.

[00:58:46] **Julia Lefelar:** Thank you.

[00:58:47] **Dr. Cristina Valencia Sanchez:** Thank you so much.

[00:58:49] **Dr. GG deFiebre:** Bye.

[00:58:50] **Julia Lefelar:** Take care, everybody.

[00:58:56] Announcer: Thank you to our "Ask the Expert" podcast sponsors Amgen; Alexion, AstraZeneca Rare Disease; and UCB. Amgen 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. Amgen believes science and compassion must work together to transform lives.

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