Navigating the International MOGAD Panel Proposed Diagnostic Criteria

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50:54 What are the gaps have been identified and will be addressed in future working groups meeting?

53:19 We are aware that the spectrum of the phenotypes in MOGAD are constantly expanding as new research emerges. How will this affect patients to test positive for the MOG antibody, but might not have the typical clinical features of MOGAD proposed in the criteria?

58:01 What if the roles were reversed? What if they have the typical clinical and imaging features consistent with MOGAD but do not have any detectable antibodies, as some countries only report a positive or a negative result? What should a physician do in this case?

1:01:16 What exciting research is being done for MOGAD that you are working on?

[00:38] **Pete Fontanez:** Hello everyone, and welcome to another MOG Cast entitled *Navigating through the International MOGAD Panel Proposed Diagnostics Criteria*. Today, we are speaking with Dr. Brenda Banwell from Children's Hospital Philadelphia, aka C.H.O.P. and Associate Professor Sudarshini Ramanathan, from the University of Sydney in Sydney, Australia. My name is Peter Fontenez, and I am the director of the MOGAD Resource and Advocacy of the MOG Project. I am the father of a daughter who was diagnosed with MOGAD for over nine years now. We would like to thank the doctors and the MOG Squad for their contributions to the MOG Cast. I'm co-moderating this webinar today with Jenny Khazan Rodrigues.

[1:25] **Jenny Khazen Rodrigues:** Thank you, Peter. My name is Jenny Khazen Rodrigues, and I'm the Australian Ambassador and Medical Professional Outreach Specialist for the MOG Project, UCB's International MOGAD Council Representative and a primary school teacher from Western Sydney, Australia. I was diagnosed with relapsing MOGAD in March 2020 after a prolonged history of recurrent optic neuritis.

[1:45] **Peter Fontanez:** This podcast is being recorded and will be available on our YouTube channel. Please feel free to submit questions in our webinar Q&A area. Any unaddressed questions will be answered in a follow-up MOG Blog.

[1:56] **Jenny Khazen Rodrigues:** One of our sponsors of this MOG Cast, Roche, has grown throughout 125 year history into one of the world's largest biopharma companies, as well as a leading provider of diagnostic tests across various common and rare disease areas. The company owns a long history of neuroscience successes with medicines and diagnostics helping patients across the disease spectrum in areas such as neuro immunology, neurodegeneration, neuromuscular disease, neurodevelopment and psychiatry. Roche's ambition is to preserve what makes people who they are and create a tomorrow where neurological disorders no longer limit human potential. To achieve this, the company collaborates with academia, scientists, patients, patient advocacy groups like the MOG Project and people like yourselves, industry partners, and clinical trial participants. With their support, there is a collective responsibility for meaningful therapeutic advances for some of the world's most difficult to treat

diseases. Roche's commitment to neuroimmunology is to develop safe and convenient medicines that reliably treat disabling diseases of the nervous system. Roche understands the impact of MOGAD on people's activities and their quality of life. Roche's goal is to further support the rare neuroimmunology and MOGAD community and collaborate on development of effective treatment and diagnostic tools to help to tackle this debilitating disease and many others. UCB, our other sponsor for this MOG Cast, is driven to ensure that everyone can live the best life they can, as free as possible from the challenges and uncertainty of this disease. These ambitions fuel their purpose, creating value in the lives of the people they serve now and into the future. Their research and development activity across neurology, immunology and other areas where their expertise aligns with unmet needs is driven by their connection to the people they serve. Their unique and diverse perspective serves as a guide and inspiration as UCB explores the furthest reaches of science and medical knowledge. They listen to and learn from patients, ensuring that their work has the greatest possible impact by delivering differentiated solutions that create value that cannot be expressed in numbers alone. They seek out tools, technologies, employees and partners that let them respond to patients needs with purposeful innovations that make a truly meaningful impact. From their headquarters in Belgium to nearly 40 countries around the world, they pursue that ambition each day, promoting a cultural of collaboration and curiosity that values diverse perspectives and backgrounds. They are committed to caring for each other, for their communities, for the planet, and for the people who inspire their work. We wish to state that neither Roche nor UCB have access nor input into the questions created for this MOG Cast, nor did these companies review or edit the faculty responses. Neither Dr. Banwell nor Professor Ramanathan were remunerated for their participation. We're thrilled to introduce our first panelist, Dr. Brenda Banwell, a professor of pediatrics and neurology Perelman School of Medicine University of Pennsylvania, and chief of child neurology Children's Hospital of Philadelphia. She also serves as the co-lead of the neuroimmune program, an innovative age span program that focuses on multiple sclerosis, MOG associated disorders and other acquired inflammatory neurological conditions in children and in adults. Dr. Banwell has over 300 scientific publications and has shared over 50 international courses focused on pediatric demyelinating diseases. Dr. Banwell leads a multi-site, North American perspective study of clinical outcomes, genetics, immunology and neuroimaging features of MS in children. She has published studies focused on the clinical characteristics of MOG related disease in children and on the MRI features of this disease. Dr. Banwell also serves as the chair of the International Pediatric Multiple Sclerosis Study Group and as a Chair of International Medical and Scientific Advisory Board of the Multiple Sclerosis International Federation. More recently, Dr. Banwell has been asked to serve as a co-lead of the MOG International Diagnostic Criteria Working Group and is a member of the MOG International Consortium. Dr. Banwell studied medicine at the University of Western Ontario, followed by residency in Pediatrics at the University of Western Ontario and child neurology at the University of Toronto. She then pursued a neuromuscular fellowship at the Mayo Clinic in Rochester, Minnesota. Dr. Banwell rose to the rank of full professor at the University of Toronto, prior to relocating to the Children's Hospital of Philadelphia in 2012. Dr. Banwell remains as an adjunct senior scientist in the Research Institute of the Hospital for Sick Children in Toronto, Canada.

We're also delighted to have here with us, Associate Professor Sudarshini Ramanathan, who is a neurologist and clinician scientist with subspecialty expertise in neuroimmunology. She is a staff

specialist neurologist at Concord Hospital in Sydney, where she looks after patients with autoimmunological disorders. She leads the translational neuroimmunology group at the University of Sydney. Her clinical and fundamental science research program is focused on understanding disease pathogenesis and improving the diagnosis and treatment of autoimmunological disorders, including MOGAD, neuromyelitis optica spectrum disorder, autoimmune encephalitis, autoimmune muscle disease, and inflammatory neuropathies. In 2013, Associate Professor Ramanathan established and has since been the lead investigator of the Australasian MOGAD Study Group, which encompasses over 150 neurologists, immunologists, and ophthalmologists from over 45 centers in Australasia. This team currently evaluates a cohort of over 700 MOGAD positive patients. We're here today to talk about one of the most exciting topics in neuroimmunology, navigating through the International MOGAD Panel proposed diagnostic criteria, where we will be diving deep into why the diagnostic criteria was created, diagnosing patients with MOGAD and limitations and challenges associated with this criteria.

[8:26] **Peter Fontanez**: I just want to welcome everybody. We're really excited to be highlighting this important topic internationally. So, let's get started, Jenny.

[8:35] **Jenny Khazen Rodriques**: We would like to begin this podcast with a little bit of background information as to why this international criteria was established in the first place. Dr. Banwell, can you please give us a little bit of background information as to why this was established in the first place?

[8:51] **Dr. Banwell:** Absolutely. So as many of you know, one of the best ways to ensure consistency of care, prompt access to care, and future research into optimal treatment for people living with any condition is to be sure you have the right diagnosis in the first place. And so the international criteria committee came together to build on existing work by some of our friends and colleagues around the world and to actually create criteria that could be applied in a way very similar to the criteria that exist for multiple sclerosis and for aquaporin-4 and other seronegative forms of neuromyelitis optica spectrum disease, for example. I will just end that comment by commenting that after the McDonald criteria for multiple sclerosis were created, and in 2010 and 2017 when they were revised, there have been numerous studies showing the positive impact of well put together criteria on patient diagnosis, speed of diagnosis, and accuracy of diagnosis. And we wanted the MOGAD community to be availed of the same level of rigor.

[10:03] **Peter Fontanez**: Thank you for that. Dr. Darshi, how essential is it to have diagnostic criteria specific to diagnosing patients with MOG antibody disease?

[10:14] **Associate Professor Ramanathan**: Thank you, Peter and thank you to the MOG Project for the invitation to speak on this MOG Cast. I suppose the first thing I'll say is reiterating what Professor Banwell said about the importance of getting the diagnosis right. With increasing research over the last decade, it's become quite clear that MOGAD is a very distinct disease entity. It's separate from multiple sclerosis. It's separate from aquaporin-4 antibody positive and NMOSD, and this matters. Getting the diagnosis right matters. There are different disease processes from a pathogenic perspective, also clinically and radiologically, but the true practical implication is getting the right diagnosis influences the treatment that you put patients on, and influences their prognosis and how you counsel patients. Getting this wrong has been demonstrated to have negative impacts on patients, because having people

with MOGAD or NMOSD on MS treatments can often result in worsening of relapses and accumulating disability. Similarly, having MS patients on the wrong type of treatment is equally damaging. So, having these diagnostic criteria specific to MOGAD is really critical in highlighting an accurate diagnosis early on, which helps inform the appropriate treatment, and in doing so, would improve the outcomes of these patients with MOGAD.

[11:40] **Jenny Khazen Rodrigues**: Thank you, Associate Professor Ramanathan for that excellent response. I would like to move on to diagnosing patients with MOG antibody disease based on the proposed criteria. How do you use the proposed international MOGAD diagnostic criteria to diagnose a patient with MOG antibody disease? Can you please walk us through the steps in a typical scenario. This is an extremely hot topic, so we would like to take a pediatric response and then an adult response. So Dr. Banwell would you please start us off, followed by Associate Professor Ramanathan.

[12:12] **Dr. Banwell**: Absolutely. And our responses are going to be similar, because this is an age span condition. It affects children and adults, but a little bit differently in the relative frequency of how a child versus an adult experience their first MOGAD attack. I think the first step in making the diagnosis of MOGAD is to start with an appropriate clinical presentation. By that I mean a clinical set of symptoms that are localized to areas where MOG would be present, so the optic nerves, the brain or the spinal cord. Patients can present with visual loss, which would be called optic neuritis. Can present with weakness, numbness, tingling, bowel and bladder or sexual dysfunction. That can refer to the spinal cord, which is called myelitis. Or, can have attacks in the brain and then the symptoms can be quite varied, depending which part of the brain is involved. But as a fairly typical example, one could have symptoms in the back part of the brain, that's just called the brain stem and the cerebellum, and someone might come in with double vision, difficulty with eye movement, and impaired balance, for example. So the first step is, is this a presentation of a relatively rapid, but not within minutes, presentation of new neurological deficits that someone did not have before. And then comes the next step of, well, what's causing that? And so the second step of our criteria is to obtain a blood sample. We use the word serum, which is part of blood, and test it for whether or not there is presence of MOG antibodies. And maybe not right this second, but a little bit later in this podcast, we'll talk about how to do that testing. And Dr. Ramanathan actually runs a lab that performs those type of tests, so she would be a better person to speak to that. The panel spent a great deal of time talking about what tests we should use to measure MOG antibodies, recognizing that the quality of an answer is very much related to the quality of the way you approach the question, and the best ways of measuring MOG matter. The accuracy of the test is influenced by that. So first you have a clinical presentation, then you need to have a positive MOG antibody test, and we can go through some of the details of that in a moment. And when we divided those MOG antibody tests, we had those that are clearly positive, which in simple terms, means lots of antibody present in the blood, versus low positive which means they're still positive. They're above the level of detection. They're different than we would expect in normal circulation, but it's a low positive result, and when that happens, there's a need for extra rigor. And so the third part of our criteria defined both clinical and MRI findings that help us be really sure that that low positive result is a true positive result for that patient. And so those specific extra steps included, how that the optic nerve, brain or spinal cord appear on MRI, for example. We also recommended in people with a low

positive MOG antibody that we also ruled out aquaporin-4 antibody disease, and advocated that those people specifically also have aquaporin-4 testing completed. And then finally, as is the case in any diagnosis, if there's a better explanation, in other words, another diagnosis fits the patient better, then that diagnosis should stand and this is the part that I think everybody has to understand. This is the part that requires expertise, and it's one of the challenges patients face if they don't see someone who's an expert in their immune conditions, because it is sometimes relatively easy to make a diagnosis, and it's sometimes much more subtle and nuanced. You need somebody with experience to be sure that MOGAD is indeed the best diagnosis for that patient.

[16:07] **Associate Professor Ramanathan:** Thank you, Brenda for that. I have pretty easy job talking about the adult version of that, because it's identical to what Brenda said. The way you'd work down the criteria, as Brenda said, spans all ages, children and adults. The only nuance that I would say is that when you look at the clinical phenotypes, that there is a difference. In adults, by far the most common presenting phenotype would be optic neuritis, often bilateral, occasionally unilateral, and subsequently recurrent. In adults, by far, over 70% to 80% of patients will have optic neuritis as the dominant phenotype, whereas in children, this can be more along the lines of acute disseminated encephalomyelitis or ADEM, followed then by optic neuritis in children. So that's the only distinction I'd make. But apart from that, the way the criteria would be worked through in an adult and a child are exactly in the order that Professor Banwell had discussed.

[17:10] **Jenny Khazen Rodrigues**: Thank you Associate Professor Ramanathan and Dr. Brenda Banwell for that excellent and very thorough response, which helps us transition perfectly into our next question. Why is it important to exclude another diagnosis when diagnosing somebody with MOG antibody disease? Dr. Brenda Banwell.

[17:28] **Dr. Banwell**: I think one of the things that we want to really be emphasized in this call is that you cannot skip steps when you make this diagnosis. And I say that deliberately, because sometimes people have a MOG antibody test ordered for reasons that aren't in that first box, the person doesn't present with a typical attack on MOG in the body. They don't have optic neuritis or myelitis. They may have other symptoms that have not yet been defined as being part of the story of MOGAD, yet they may have a low positive MOG result. Then we have a patient with a lab test, but not the clinical story to fit with the diagnosis. And that's one of the biggest challenges in medicine, which is when a test is ordered outside of the regular indication, and can lead to a great deal of difficulty. And frankly, most of the time in that situation, there is indeed a better diagnosis. Because the patient doesn't show signs that their immune system is attacking MOG they may have many other symptoms going along. The humility of that answer, though, is that we continue to learn over time that diseases can have a broader range of symptoms than we originally appreciate. And with that in mind, I think all of us in the MOG community want to follow patients who have borderline or even clearly positive MOG results, but who don't present in any of the ways we recognize currently as being associated with MOGAD. We want to determine whether or not their subsequent course and story fits with a disease that looks like the immune system attacking in areas where MOG is present. So to your specific question, why is it so important? It's pivotal because the next step after diagnosis is treatment. And treating patients with MOGAD, we're going to talk in a couple of questions about the difference between a single attack in patients that might only have one event

versus relapsing MOGAD. But the treatment, either acutely only or chronically, requires that you're treating the right disease or you're potentially exposing someone to treatment that they won't benefit from and definitely don't need.

[19:39] **Peter Fontanez**: Thank you for that Dr. Banwell. If a patient or their caregiver believes that they or their child has MOGAD based on their symptoms and presentation, what is the best way to talk to the physician about this in order to get evaluated properly?

[19:54] **Dr. Banwell:** Sure. So, I mean, I'm a firm believer in having a frank and open conversation with all of my patients, and I would hope that would be the same in reverse. I hope that's true of all my colleagues. Many of my patients, by the way, have come in not necessarily with diagnostic questions, but with new information about a treatment they've read about, or something they're keen to share, and that's the key part of a doctor-patient relationship, is that you communicate. To someone who's out there living with what they believe might be MOGAD, and perhaps have not yet seen an expert for that diagnosis, or maybe they're very new to their symptoms, and they've already gone online and recognize that it sounds a bit like MOGAD. I encourage people come with a couple of the links or references that describe the symptoms, in case, the doctor that they're working with, or nurse practitioner or other health provider is less familiar. You know, particularly in communities where the first physician or advanced practice provider that you see might not even be a neurologist. Not everybody lives within a few miles of a neuroimmune expert. In fact, most of the world doesn't. So thinking about conditions that are rare like MOGAD means that sometimes the patient has as big a role as their clinician in the early steps of bringing this idea forward so that that can be properly explored.

[21:15] **Peter Fontanez**: Okay. A follow up to that with a community question. In what case should a patient pursue an appointment with an expert for a second opinion?

[21:26] **Dr. Banwell**: Anytime. I think patients should have a second opinion anytime that they or their physician feel that the diagnosis that they're looking at is either unclear. Or, the team looking after a patient has relatively limited familiarity with the condition and would welcome an expert opinion to help partner. It’s not taking over necessarily, just partnering with a care plan for that patient and their family. When there's confusion and differing opinions then sometimes going to someone who sees a great deal of patients, a large number of patients with MOGAD and related conditions, is incredibly helpful. Sometimes that's the type of expert that can pick up the one, little subtle finding that really helps you get to the right final answer. So, I think second opinions are incredibly important. I think it's not always practical to travel. I realize that's difficult, and I wish we had even better access to telehealth for families living in more remote regions. But having them, or ideally even their doctor can easily call another physician to say, help me out. And can we talk through this patient story so that you can give me some general guidance on where to go next. And I think all of us do that quite a bit.

[22:42] **Jenny Khazen Rodrigues**: Thank you Dr. Banwell for those very thorough responses. The next question is a very important question, and it's one of our extremely hot topic questions. So we are aware that the panel elected not to diagnose MOGAD on the basis of MRI alone, but rather focus the first part of the criteria on the clinical presentations. Can you talk to us a little bit about why this decision was

made? This is an extremely hot topic. Associate Professor Ramanathan, if you would like to answer this question.

[23:14] **Associate Professor Ramanathan**: Thank you, Jenny. The diagnostic criteria were designed to be of clinical utility to clinicians, patients, and clinicians who may or may not be expert in the field of demyelination. I think it had to be presented in a way that makes clinical intuitive sense. So when patients present, they present with symptoms or clinical phenotype. They don't present as a scan or a radiology appearance. If they come in with eye pain and loss of vision, then we think of the syndrome of optic neuritis. If they present with paralysis of the lower limbs or sensory disturbances or bladder or bowel dysfunction, we think of myelitis. And this is a combination of their history and their clinical examination. I think first and foremost, in our minds, when we assess a patient coming through the emergency department or in our clinic, we're formulating what kind of syndrome do these patients fit under? Not necessarily exactly, what is the diagnosis, but what's the clinical syndrome. If that syndrome is suggestive or makes one think about MOGAD, for the reasons we've discussed before, then we subsequently go into the other steps of the diagnosis. Now, in the footnote of the diagnostic criteria, certainly there are radiological clues. A diagnosis of optic neuritis may be supported by certain radiological features, and a diagnosis of myelitis may be supported by certain radiological features. But first and foremost, the patient comes in with a clinical presentation, and so the clinical phenotype and supportive radiology is what we look at in the criteria. As Brenda spoke through, we have the clinical presentation of demyelination and then we have an antibody test. I guess where MRIs play an important part, is in that part that Brenda discussed briefly about supportive criteria. This is for patients, if we've defined them as having an antibody test that's a clear positive. Which is defined as different laboratories performing these gold standard diagnostic tests by live cell-based assays having different meshes, but they often have a threshold, and then they have a subsequent threshold where patients above that level are a clear positive. And in those patients, we don't need any more supportive criteria, apart from those core demyelinating syndromes in the blood test. But for the patients who are what we call low positive, all patients in whom an antibody titer isn't reported or in patients where they don't have MOG antibodies in serum, but they do have it in the cerebrospinal fluid, which is more unusual. What we recommend is that we then use supportive criteria. And those supportive criteria are both clinical features, but also radiological features. And so here an MRI is really important. If someone has a MOG antibody consistent phenotype and a low positive antibody result, and then the optic nerve or spinal cord imaging, MRI, shows supportive features that's very helpful to make the diagnosis. Thank you.

[26:20] **Dr. Banwell**: Yeah, if I could add one comment to that, which is an excellent answer and very thorough. I think your question, Jenny was a little bit about, why not start with the MRI? Someone has an MRI and you say, oh, that's MOGAD, and that's the right way to go. A couple of comments. Unlike multiple sclerosis, to the best of our knowledge, we have not yet identified patients who have MRI features of the immune attack on myelin, who have not yet had any MOGAD attacks. I'm not saying it's impossible, but to my knowledge, that's not yet been described. And the reason that's important is because in between MOGAD attacks, only 3% in one study and I think it was 5% or 6% in another, of all scans looking at 1000s of MRIs were there silent new lesions. In other words, new areas of attack that came on the MRI between the clinical attacks in a patient with MOGAD. In other words, the MRI is not a

good barometer. It's not actually the place where new and surprising findings show up in MOGAD. So we didn't start with MRI because we would have missed most of the patients for one and it would probably have led us down the wrong path. In multiple sclerosis, which is completely different disease, one of the hallmarks of multiple sclerosis is that you can see lesions before the patient has their first attack. If they happen to have an MRI for another reason, and we have a silly term for that, in my view, but radiologically isolated syndrome, which is kind of a funny word, it's not a syndrome and it's just an MRI that was done, perhaps for headache, and the MRI looks like MS. Only a portion of those patients, but a high proportion will go on and eventually have an attack that clarifies that this really is multiple sclerosis. But in between attacks in multiple sclerosis, there are often lesions that, especially untreated patients, will have many new MRI findings that help you see this dissemination in time. In other words, new lesions over time. That is not a characteristic of MOGAD. So we didn't start with MRI in our criteria, because MRI plays a supporting role in looking at how the attack occurs in MOGAD, the length on the optic nerve, the distance of the spinal cord, the appearance in the brain. But it's not like MS, where you might pick it up earlier, because you have an MRI, at least to the best of our knowledge, that was done for a bump on the head, and you had an MRI and now somebody is questioning MOGAD. Does that make sense? I'm trying to explain why we didn't start there, because the best place to start in any diagnostic journey is with the appropriate clinical symptoms, because then you're much more likely to follow the correct path.

[28:51**] Peter Fontanez**: Thank you for that Dr. Banwell, yeah, that makes a lot more sense. You were touching on multiple sclerosis. Dr. Banwell, this is actually a hot topic in the community, and since you touched on that, let's continue with that. Since the release of the proposed criteria, we have seen more patients come to the MOGAD community who were recently diagnosed with multiple sclerosis and are now currently diagnosed with MOGAD and vice versa after further investigation. Is this a good step for understanding the diagnosis of MOGAD? Why or why not?

{29:20] **Dr. Banwell:** Sure. So I think it's an excellent step, because again, back to where we started, the best diagnosis, the most correct diagnosis, is going to allow us to optimize the appropriate therapy, and they're not identical. So that's step one. I think a couple of points on making the diagnosis of multiple sclerosis versus MOGAD. We frequently talk about our diagnostic criteria at the day that we meet the patients and their family, like the first attack, and we look at their clinical symptoms, we look at their lab result, we look at their MRI. One of the best ways actually to tell MOGAD from multiple sclerosis is actually over time, because in multiple sclerosis we see an increasing number of new lesions and very you know, fairly typical locations. We see lesions that were there before staying and persisting, sometimes even slowly expanding. We see lesions that enhance fairly frequently and other features over time. In MOGAD, very happily, as I mentioned before, we typically don't see a lot of new lesions, and in fact, very rarely see lesions separate from events. By lesions for those on the call that don't know what a lesion is, I mean an area that's bright on the MRI scan that shows us where there's inflammation and attack on MOG at that location in the brain or the optic nerve over the spine. In patients with MOGAD, those changes often get better with time. They get fainter. In some patients, they almost go away. It's not uncommon for a patient with MOGAD, for example, who may have had optic neuritis and a few changes in the brain to have an MRI two years later that no longer shows any brain lesions. That would be highly

atypical for multiple sclerosis. So it's really important that sometimes making the right diagnosis is more evident after a little bit of time. When you see the evolution and change and the cadence of the disease, sometimes we see this divergence, where patients with MOGAD and patients with MS look more and more different over time than they did at the beginning. So that's just really important, because not everything in every patient works perfectly on day one, and sometimes you just need a little bit of time to start separating the two conditions. And that is one of the reasons that people are now being tested for MOG IgG who have carried the diagnosis of MS for a few years, perhaps, and don't look like MS anymore. And their clinician might be saying, hey, I wonder if this diagnosis is not right for you. Then they test for MOG IgG, and the patient has, hopefully a clear positive, which makes it easier to be sure, where you can then say, actually you have MOGAD. And I think that, of course, will happen with the recognition of MOGAD as a condition.

[32:05] **Jenny Khazen Rodrigues:** Thank you, Dr. Benwell, for that very vital response. As you all know, clinical trials are relatively important for MOGAD, especially when there's no FDA treatments specific for this disease. How will the proposed diagnostic criteria refine the inclusion for participation in the clinical trials? Associate Professor Ramanathan.

[32:27] **Associate Professor Ramanathan:** Thank you, Jenny. So clinical trials are key in the field of neuroimmunology to try and move things forward, and particularly to try and identify more targeted treatment approaches that might remove the focus from general immunosuppression to more focused immunosuppression. I think a key concern with clinical trials is ensuring you have the right population enrolled or recruited into the trial. And what is a real concern for many clinicians, is having patients, and because of the nature of rare disease. These trials to occur as a stage phase three randomized control trial are often International. Require 10s of sites, 50, 60, 70, sites worldwide to be able to recruit the numbers needed for a definitive answer. And what we're really concerned about is having patients who did not have MOGAD incorrectly recruited into these trials. And specifically, the population of concern is somebody, for example, with multiple sclerosis, being enrolled into these clinical trials. And this is a particular concern in that category of low positive serum MOG antibody result, not so much using a live cell-based assay, but this is certainly a concern using a fixed cell-based assay, which is often more globally and widely available. So having a low positive result of a fixed cell-based assay in a patient with MS is a presentation that many of us are dealing with, and we often get asked by colleagues that this person who's got a MOG antibody positive result and doesn't look like MOGAD and looks like MS. This kind of reiterates the point that Brenda made, that if the scan looks like MS, then you should not be thinking about MOGAD. And I think the diagnostic criteria help with clinical trials because of that stringency of the criteria and the emphasis on being specific to the diagnosis of MOGAD. I'll draw your attention to the last part of the diagnostic criteria, which is exclusion of a better diagnosis. So you could potentially have an MS patient with a low positive result, and who has optic neuritis or a transverse myelitis. But the key factor is if they have other features consistent with MS, then they most likely have MS and not MOGAD. So, the diagnostic criteria emphasize specificity of these criteria for MOGAD and try to eliminate patients who do not have MOGAD being included. And this is really important for, I suppose, the integrity of the trial, and also for results that we can interpret, and which are applicable to the MOGAD community.

[35:11] **Peter Fontanez:** Thank you for that. Real quick community question for Dr. Darshi, how is a high positive defined?

[35:20] **Associate Professor Ramanathan:** This is a complex question, because the assays that are used use the same principle, and essentially a cell based assay has an in vitro system, which means within the lab, in tissue culture plates that you can express cells that have MOG expressed on the surface of them, and you incubate this or put this together with patient serum. We have different methods of identifying the degree of antibody binding from a patient's serum compared to a healthy control, for example. Now the live cell-based assays, which are the gold standard diagnostic with a very high specificity and sensitivity. Which means that they're very close to 100% in getting a MOGAD diagnosis, and they don't miss many patients. These are available in research centers globally, but there are a few research centers, and so not everybody around the world has access to these. The more commercial assays are more widely available, but because of the way that the assays perform for distribution, it has reduced specificity and sensitivity. So, I suppose how you define a clear positive is a little bit tricky, because you'd have to find a way that takes into account the specific protocols of different laboratories. But essentially, the very validated research groups have performed significant validation of their assay to try and ensure the highest consistency with their results. And what these groups have is identified a threshold of what you'd expect the healthy population or other non MOGAD diseases to be below, and a threshold above which it's a concern. A clear positive is defined as being two standard deviations above that threshold, so it's very high antibody result based on that specialist laboratories assay. So, a clear positive is over two standard deviations above that threshold, and that means that those patients almost certainly have a diagnosis of MOGAD in combination with the appropriate clinical presentation. If it's between the threshold and below two standard deviations, that's what we call a low positive result. That's the unifying way of identifying what's a clear positive versus a low positive. It's tricky, but hopefully all the laboratories are going towards being able to provide that indication in their reports now of whether or not a sample is clear positive by their laboratory standards or a low positive, and that should help to enable clinicians to go forward with the criteria.

[37:56] **Jenny Khazen Rodrigues:** Thank you, Associate Professor Ramanathan for that excellent response. I just want to go back a little bit to clinical trials. Dr. Brenda Banwell, are we going to be seeing any pediatric clinical trials anytime soon?

[38:12] **Dr. Banwell**: I think yes. Several trials are in design. One of the things that may help us in the pediatric community. Let me take one step back, so clinical trials are difficult. I think we want everybody to understand that they're incredibly expensive to do, and in rare disease space like MOGAD, as mentioned by Dr. Ramanathan, they require many, many places around the world to be to enroll enough patients to be completed. It's important the community understand this, because the only way trials will be completed is if it's a good trial that the community endorses and participates in. So that's going to be fundamentally important for us as clinicians to work to design those trials so they meet the needs of our community, and for our community to feel that it is important to participate. And people have different views on that. With that caveat, the next challenge with a clinical trial is whether or not we have an adult trial only and then wait to see the results of a new medication and then bring the trial to children. That is how most medications are studied worldwide. The studies are done in adults first, provided the

condition effects children and adults, of course, and then only after all the data has come in, the outcome, the benefit and the safety, then the trial is brought under age 18. Problem with that model for the pediatric MOGAD community is that means that they wait to gain access and knowledge and understanding of any potential trial all the way through the first adult trial. Then we enroll the pediatric trial, and then we wait three to four years to get those results. And inherently, pediatric patients would be many years behind the adult patient community in gaining access to FDA or other national agency approvals around the world. So, in the aquaporin-4 NMOSD, not necessarily aquaporin 4, pardon me, in the NMOSD trials, in which most patients had aquaporin-4, there were a couple of trials that included teenagers in the actual phase three or the big trial. And I'm hoping that in the MOGAD studies, we will be able to do the same, which will at least help bring the teenage population forward more quickly. And that would be very important. I will also make the point that when we're looking at relapsing MOGAD, which is what these trials will be for. These trials are not going to be for patients that have only one attack, because, of course, as we all know at least half of patients with MOGAD only have one attack lifelong. So, we don't need to put them on a chronic therapy that they take for years if they don't have relapsing disease. So, in patients that have two or more MOGAD attacks, I anticipate will be the population going into any of these trials. The relapsing MOGAD population, at least by the time they declare themselves as having relapses, often, is over 12 years of age, not entirely, but quite often. So hopefully, we'll be able to get that group of children into the original pivotal studies that will come forward for all of the MOGAD patient population, pediatric, adolescent and adult. And there are several studies that are well on their way for design and hopefully will be enrolling soon. There may even be one starting enrollment now, although I think there were still some plans going on to that study.

[41:35] **Jenny Khazen Rodrigues**: Thank you, Dr. Banwell, for that very thorough response. I would like to move on to the limitations and challenges associated with the proposed MOGAD diagnostic criteria. As you are aware, not everybody around the world has access to the same tools used to make the diagnosis of MOGAD, such as MRI or MOG antibody testing on a live cell-based assay. What should a physician do in this case to make the most accurate diagnosis possible? This is an extremely important question. Dr. Banwell, if you would like to start us off, followed by Associate Professor Ramanathan.

[42:09] **Dr. Banwell:** We know that is going to be a challenge, and that's, in fact, a very big driving reason why the criteria have a strong clinical description, include the possibility that someone may have a positive MOG result that could be by a fixed not necessarily a live, cell-based assay. And the fixed assays are more portable, so more centers around the world have access to them. Even if they're not, comparatively, might not be quite as sensitive as the live cell-based assay. Many places don't have live cell-based assays. So, if the fixed assay is positive, and sometimes we don't even have a titer, that's where the supplemental criteria come into play to substantiate the diagnosis. That still requires that the patient had the assay measured. Right this moment it is not possible, according to criteria, to make the diagnosis of MOGAD in the absence of evidence of MOG antibodies being present in that patient. And you can't start criteria looking at a disease that is pivotally associated with MOG antibodies. If your initial criteria don't require MOG antibodies, we would never get to the ability to define our patient populations, learn more about the disease, design trials, look at therapeutics. If our original criteria had not required that we had MOG antibodies as part of the criteria. I hope I'm being clear, without defining

your core population really well for now and for the future, you can't then go back with confidence to say, okay, now we know about MOGAD really well. Here's a patient living in a country where the assay is unavailable, but they have the clinical features and supplemental, supportive features. That's enough. We are not ready to do that. We don't have evidence that that's enough stringency to be sure that the person actually has MOGAD, and therefore we can't confirm that diagnosis at this time. So, in places where the testing is unavailable, unfortunately, so too is the diagnosis at this stage.

[44:20] **Associate Professor Ramanathan:** What I would also add to that, Jenny, is that I think it's a really critical problem. The onus is on the research groups, I think, internationally, to be able to try and increase our collaborations with regions of the world that currently don't have access to some of these assays to be able to provide the training and the supportive infrastructure for these assays to be more widely available. And I think that many of the research groups are certainly trying to optimize the way these assays run to a more efficient system that might require less staff and less time and less infrastructure. So that we can try and translate these highly specific and sensitive results, but also train regional centers or geographical locations that don't currently have access to be able to provide this at a more local level. To prevent the requirement for shipment and so on. I also think medicine in the developing world is often performed on a pragmatic basis. I think that the people who this is their job, and day in and day out, and they manage their patients as well as they can with the resources available. It is on us to use these criteria. And as Brenda said, we're not there yet, but eventually go towards a position where we can further enhance the clinical radiological tools that enable people to make these pragmatic decisions and manage therapy at this level, given what they've got available to them at that point in time. So, I think those are the only two additions I'd make to the answer.

[45:52] **Dr. Banwell**: I guess actually commenting just slightly on that extension. Of course, you know we're talking about criteria that assume clinical expertise of confirming optic neuritis or myelitis, which is not universal. We've talked about the trouble with the assay, but there are many parts of the world where people have absolutely no access to MRI either. A CAT scan might pick up optic neuritis reasonably, but certainly is not going to pick up some of the lesions in the brain. It's just not a good image tool for demyelination. It's just simply not going to pick up myelitis in the majority of patients. So again, you know, depending on the world region we're referring to, there are challenges well beyond just the assay in terms of making a diagnosis of MOGAD or MS or neurosarcoid, or any one of a number of conditions that may be impacting that individual in a country where the condition is potentially even more rare than in parts of the world where we have more resources. But we obviously don't know that answer, because something only looks rare if you don't actually find it.

[47:03] **Peter Fontanez:** Thank you both for those answers. Those are very thorough answers. Can you talk a little bit more about the need for clarified multiphasic disease language, the definition of a relapse versus a flare up, and how the working group will address this in the future versions of the proposed criteria? Dr. Banwell.

[47:22] **Dr. Banwell**: Certainly what a lovely question, thank you, Peter. I think the first step that we took with the criteria was that we defined a separate clinical event, and we did use the word relapse as being more than 30 days from the prior event. We did not choose to follow the criteria proposed previously for

children with ADEM, where we said that a second event really ought to be 90 days out. Because some of the children with ADEM that we've all looked after kind of fluctuate for a window of time around their presenting illness. But we very explicitly made the point that the new set of symptoms needed to be distinct, not just fluctuations from the initial symptoms and more than 30 days from the prior event. There's no crystal ball way to know for sure whether that's the best way to do this, or whether we should have a longer window of time to define whether somebody is having more than one discrete attack. In other words, their immune system is remaining active against MOG versus those patients that very clearly have one event, they improve, the prior changes often disappear and they don't have any further attacks. And for some of us, we have patients that are now 10-15 years, we didn't know it was MOGAD 15 years ago, but we had samples from them from 15 years ago, and we were able to go back and test that and see how those patients have done now. So, there are many groups that have patients that have been followed closely, that we know had MOGAD or MOG antibodies and MOGAD presentation 15 years ago, and have clearly not had any new MRIs changes and no further attacks. I think we can confidently say to the best of our current ability of duration of follow up, that monophasic or a single attack does exist, versus a smaller proportion of patients in most studies that actually have relapsing disease. What we don't know, and I think we're all aware of this is we do not know whether MOGAD is a lifetime disease. We know that MS is. There's years and years and hundreds of years, actually if you go back far enough to the original Charcot descriptions of MS, where over 100 years plus of observation that is like multiple sclerosis is a lifelong disease. To the best of our knowledge, aquaporin-4, neuromyelitis optica spectrum disease does not go away. We really don't know whether MOGAD can have relapses for a period of time and ultimately no longer have attacks over time. We don't know that answer. We know that there are people who looking back in time, had a MOGAD presentation, maybe had a second attack, 3, 6, 7, months later, and then nothing for another decade. We know that those people have not had any further attacks, and at the time, they weren't diagnosed with MOGAD, because I'm talking about patients that were in studies years ago. So only now do we know that they had MOGAD, but they've been followed all this time. So I think a big unanswered question, and what we're going to rely on the MOGAD community, it's all of you that are going to help us answer this question. We need very careful, long term follow up of people diagnosed with MOGAD so that we can understand whether this is a lifelong disease or a transiently relapsing condition in some people, as well as a monophasic illness and others. I don't use the word flare up, by the way, just to answer that question. I don't find that a helpful term personally, it's not in the criteria.

[50:54] **Jenny Khazen Rodrigues**: Thank you Dr. Banwell. What are the gaps have been identified and will be addressed in future working groups meeting? If you could please answer this Associate Professor Ramanathan.

[51:06] **Associate Professor Ramanathan:** Thanks, Jenny. I think the diagnostic criteria group are continuing to meet, and there's a very strong appetite for continued network for international collaborations in MOGAD. And I think the more you meet, the more you identify possible topics that you could be working on together. And I think you know definitely gaps in knowledge include, you know, firstly, validating the diagnostic score prospectively is going to be very important for us. To be able to see how they perform and potential strengths and future improvements. I think learning more about the

longitudinal radiological profile of this condition is important. Early work has often focused on the radiology of the first presentation, and we're trying to identify potential prognosticators for long term outcomes on cognition in patients and children with ADEM, for example, in adults with brain involvement, etc. I think better understanding the pathogenesis of MOGAD is something that is a real gap at the moment in conditions like NMOSD, where we've had the benefit of time and very good animal models that translate better than we've had luck with in MOGAD. This has been, an area that has progressed significantly. At the moment, studies in MOGAD disease pathogenesis are early and still ongoing, but I think this is a really important area, because this is how you identify potential treatment targets. And then I think, essentially, treatment is the big elephant in the room. And how do you optimize treatment at disease onset? Is there a way of, you know, modifying future risk of relapse in patients who are relapsing? What is an appropriate way to move forward? And how do we manage these in patients, even with relapsing MOGAD, there long gaps between episodes. And so it is a very different disease process. And so I think treatment and treatment regimens are a very important area for future research.

[53:19] **Peter Fontanez:** Thank you for that Dr. Ramanathan. We are aware that the spectrum of the phenotypes in MOGAD are constantly expanding as new research emerges. How will this affect patients to test positive for the MOG antibody, but might not have the typical clinical features of MOGAD proposed in the criteria? Dr. Ramanathan.

[53:39] **Associate Professor Ramanathan:** Thank you, Peter. I think a key point of this question is, why are we testing these patients? Or, you know, why would a clinician want to test a patient for MOG antibodies? And an important point in the diagnostic criteria is towards the end, where we make recommendations on who we should be testing for MOG antibodies. So, I guess the first part of my answer is that really careful decision making about when we test MOG antibodies is really important. We recommend testing MOG antibodies in all children with demyelination under the age of 11, because it is a very common cause of demyelination in children. But we certainly do not recommend MOG antibody testing in all adults with demyelination, because by far the majority of these patients will have multiple sclerosis. We recommend testing for MOG antibodies in patients in whom there is a suspicion of MOGAD, based on those clinical and radiological criteria we discuss. The reason this is important is that an assay is an assay, and no matter how specific and sensitive it is, there could be a percentage, a few percent, of false positives or false negative results. What happens when you have a large group of patients tested with a low pre test probability of MOGAD, is you increase the number of false positives. So, you increase the chance of getting a result that doesn't necessarily have a clinical utility and this can lead people down the wrong management perspective. So, I think it's quite important to know why you're requesting a MOG antibody test in the first instance. The part of your question that referred to people with a rare clinical phenotype. What I would say to that is that less common but well recognized clinical phenotypes in MOGAD, such as cerebral cortical encephalitis and aseptic meningitis and so on, have certainly been identified in patients with MOGAD, but these are in patients that have been established as MOGAD positive for particular reasons. So, I think your point of concern is that somebody with a rare phenotype might be missed. But my answer to that would be that you wouldn't want to be testing anybody with neurological symptoms for MOGAD because of the risk of having a high number of

superfluous results. And I think that these less recognized MOG antibody phenotypes do come out in the wash and we are increasing our awareness. Once again, with the humility that Brenda mentioned, this is an ever-evolving field, so things that we don't recognize at the moment will soon become apparent with the passage of time and bigger cohorts.

[56:18] **Dr. Banwell:** Yeah, and I 100% agree with that. And I think you know the cortical encephalitis one is a phenotype that is, I think, more recognized even now than it was when we wrote the criteria, not that many months ago. And this is important, because the management of patients with a cortical encephalitis, especially if they have brain swelling, can be very, very emergent. You have to recognize that this person has an inflammatory illness. You're not going to know the MOG results in those first 24-48 hours in almost any center, because MOG testing is not done at most centers. It's a reference lab test. We don't run it at my hospital. We send it to a reference lab in the United States. And so it's a clinical suspicion in that scenario to think about the patient's condition being highly inflammatory and potentially a MOGAD presentation. And so we are going to learn more. And the purpose of having criteria is that they are constantly living. The criteria are not static. It's not that we got it right the first time and everything's going to be perfect thereafter. We all recognize that it's a starting place. And from a starting place, you refine, you add or you subtract, if we're wrong on something and we learn. But we spent many, many hours, 72, meeting to talk through the creation of those criteria with people who see patients with MOGAD on a daily or weekly basis to try to come up with the best first attempt that we could do. And we recognized that as soon as it was printed on paper, there's going to be people that will come to us with changes, and that will be version two down the road.

[58:01] **Jenny Khazen Rodrigues:** Thank you, Associate Professor Ramanathan and Dr. Brenda Banwell for that very important response. What if the roles were reversed? What if they have the typical clinical and imaging features consistent with MOGAD but do not have any detectable antibodies, as some countries only report a positive or a negative result? What should a physician do in this case? Dr. Banwell.

[58:23] **Dr. Banwell:** At this precise moment, if you do not have confirmation of MOG antibodies, we cannot confirm MOGAD. At this moment, that doesn't change how a doctor and patient interact and talk about how to manage the patient's inflammatory brain condition, but in terms of the stringent answer to your question, without confirming the diagnosis, by having MOG antibodies detected, we would not be able to confirm the diagnosis. What I would do if I have a patient that was who came to me, who has a result from wherever they came from that was not reported or the didn't have the testing done. The first question is, were they tested early enough? And if the answer was that they were tested at the time of their first attack, and the test was a live cell-based assay in a lab that has a high accuracy rate, in other words, is a lab that does the test a lot and is a well-recognized reference lab, then they were negative at that first event. Most studies would suggest that they probably are negative. What can happen easily, though, is that MOG antibody testing might not have been done early. Therefore, by the time the person is tested, it could be 6, 12, 24, months after their event. MOG results, or MOG titer, so the amount of antibody and blood go down over time in almost all patients, and so if you test them further away from the beginning of their disease, you could get a negative result, but it would have been positive if you'd had a sample tested earlier. So that is a living reality that hopefully will improve with increasing

recognition of performing the test promptly. And then the other important situation that can occur is someone is treated immediately, emergently, urgently, which might be very important for them. Sometimes even be treated with something called plasma exchange, which basically will pull out of the bloodstream the MOG antibodies. And then someone recognizes that MOG might be a possible diagnosis, and they try to test, then at that point, the testing might well be negative, because the treatment, the plasma exchange, which was given because of the severity of the person's presentation, may have rendered the blood clear of the antibodies and therefore you won't get a result. In those individuals sometimes, spinal fluid can still be positive. And so that would be one of the situations where a spinal fluid test for MOG antibodies might be reasonable. Keeping in mind that that is still largely a research test and not a clinically available assay. And so it gets complicated. In that situation, you really do need to speak to someone who's an expert in order to try to make the diagnosis in that situation. It is absolutely difficult if someone is tested either after treatment, particularly PLEX, or well into their disease course when they are quite some distance from the first event.

[1:01:16] **Peter Fontanez**: Thank you for that answer Dr. Banwell. We will finish off with one last question, the future of your of your research and MOGAD as a disease. Every year we continue to learn more about the MOG antibody disease, as research continues to grow. What exciting research is being done for MOGAD that you are working on? We are excited to hear from both you, Dr. Ramanathan and Dr. Banwell.

[1:01:39] **Associate Professor Ramanathan:** Thank you, Peter. So, I guess some of the things that my research team are interested in looking at, firstly, trying to better understand underlying disease pathogenesis in MOGAD and so number of basic science projects with our collaborators that we're working on this. Secondly, and very importantly, is the identification of biomarkers for disease prognosis, whether it's clinical, radiological or laboratory, serological biomarkers to try and identify, you know, is this a patient who's going to have a monophasic presentation? Is this a person who might be at a higher risk of relapsing disease? And I think that's something that's quite important. And then finally, and very importantly, I think trying to identify appropriate or optimal therapeutic regimens at disease onset and disease relapse is something that we're actively looking into.

[1:02:35] **Dr. Banwell**: And then I guess I will add to everything that Darshi said, I agree 100%. I mean we're both clinicians first and then our research adds to our clinical acumen. So first and foremost, I care about, you know, having a really good understanding of my patients and their journey and what they and their family experience. That's going to edify everything we do coming down the road. But in terms of, you know, other areas that are really important, we're trying to look at what the immune system in MOGAD actually does. So, it's not just the MOG antibodies. There are also MOG reactive T cells. And for those of you who don't study blood, our immune system has different parts to it. There's the B cell component that makes what we call antibodies, and that's what we test, which is the MOG antibody in the blood. But there are also active cells, effector cells, we call them, that are a different arm of the immune system that can also gain access into the brain, around the optic nerve or the spine, and are probably just as important, perhaps, than the MOG antibodies that call the immune system to the places where MOG is present. We hardly study those because they're in a low number in circulation. It's very difficult to study MOG T cells. It's not something a routine clinical lab can possibly do. It requires very

specific testing and very unique laboratory work. But it needs to be done. We need to know what those cells are doing, and we need to know what proteins inside those cells, and we use one of the groups of those proteins are called cytokines, and what does that profile look like? And that is pivotally important, because one of the treatments that is changing the course of neuromyelitis optica spectrum disease is recognition that interleukin-6, which is a cytokine, if you target that and bring that down by blocking interleukin-6 receptors, you improve the prognosis of patients with NMOSD. This is important because patients with MOGAD appear also to have high interleukin-6 levels, particularly in spinal fluid. So, we need to do this research because it will guide some of the upcoming clinical trials, and there are medications that might be very appropriate for patients with MOGAD that target this biology. And so I think one of the most exciting and important things we can do as a community of scientists and clinicians is define what an investigation for a child or an adult with MOGAD should include. What we can do and recognizing that not every center has every toy and every tool but we share many. I think if we as a community define pretty quickly what tests we want to do and collect consistently, we're going to be able to really have the information we need to look at some of these potential molecules that can be targeted as therapeutic strategies in MOGAD.

[1:05:21] **Jenny Khazen Rodrigues:** Thank you Associate Professor Ramanathan and Dr. Brenda Banwell. Finally, we would like to say a massive thank you to our wonderful experts, Dr. Brenda Banwell and Associate Professor Darshi who have taken the time to navigate us through the newly proposed international MOGAD diagnostic criteria. We definitely look forward to continuously seeing more of the International MOGAD diagnostic criteria in action.

[1:05:46] Thank you. Thank you.

[1:05:49] **Peter Fontanez:** Any unanswered questions will be collected, answered by the doctors and made available in a follow-up Mog Blog for this event. The podcast will be available on our YouTube channel also. Thanks for this great discussion, and we wish you luck in your research. Have a great rest of your day.

[1:06:04] Thank you everybody. Thank you so much. See you all later. Thank you good night for those in Australia.