CURE Epilepsy Webinar

Epilepsy with Eyelid Myoclonia (EEM), Formerly Jeavons Syndrome: Diagnosis and Treatment

(Transcript)

Dr. Laura Lubbers: Welcome, everyone to today's webinar. I'm Laura Lubbers and I'm the chief scientific officer of CURE Epilepsy, and I want to thank you for joining us today. Today's webinar is entitled Epilepsy with Eyelid Myoclonia: Diagnosis and Treatment of this Rare Photosensitive Epilepsy. Epilepsy with Eyelid Myoclonia or EEM is also commonly referred to as Jeavons syndrome. This form of epilepsy is a type of absence epilepsy characterized by a brief but intense and repeated fluttering or jerking of the eyelids. The seizures associated with this type of epilepsy can be triggered by bright and or flickering lights and can be associated with an abnormal EEG pattern. CURE Epilepsy recently convened an international group of experts to address unmet needs regarding the diagnosis and treatment of EEM. This group of experts led by doctors Kelsey Smith and Elaine Wirrell used a process called a modified Delphi consensus process to survey experts from around the world, to develop a better understanding of the clinical presentation of EEM and establish best practices for its management.

This seminar kicks off the second half of the 2023 CURE Epilepsy Webinar series where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website and YouTube. You can also download transcripts of all of our webinars for reading. CURE Epilepsy is proud to celebrate our 25th anniversary this year. Since our founding in 1998, we've raised millions of dollars to fund epilepsy research that supports our mission, which is to find a cure for epilepsy by promoting and funding patient-focused research. CURE Epilepsy provides grants that support novel research projects and advance the search for cures and more effective treatments. Today's webinar will help attendees learn how to recognize the clinical features of EEM as well as how to differentiate it from other epilepsy syndromes. The webinar will also review the consensus first-line treatments for EEM.

This webinar is presented by Dr. Kelsey Smith, who is an assistant professor of neurology and an epileptologist at Mayo Clinic in Rochester, Minnesota. Her clinical and research interests include genetic generalized epilepsy syndromes such as EEM, autoimmune-associated seizure disorders, and women with epilepsy. She's the first author of multiple publications that address the diagnosis and treatment of EEM. Before Dr. Smith begins, I'd like to encourage everyone to ask questions. We'll address the questions during the Q&A portion of the webinar. Keep in mind, you may submit your questions anytime during the presentation by typing them into the Q&A tab located on your Webex panel and click send. We'll do our very best to get through as many of the questions as we can. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. So with that, I will turn it over to Dr. Smith.

Dr. Kelsey Smith: Great. Thank you so much. Thank you to CURE Epilepsy and to Laura for having me here today. I'm really honored to give this talk today on Epilepsy with Eyelid

Myoclonia and we'll discuss the diagnosis and treatment of this rare photosensitive epilepsy syndrome. And as Laura already stated, I'm an assistant professor of neurology and an epileptologist at Mayo Clinic, and really excited to be here today to give this talk to you about this important topic. All right, let's see. I don't think I'm controlling the slides. Sorry, let's see. Clicked it. Okay, I'll take control. Okay, hopefully this should work.

Okay. So just to start off with an acknowledgment and disclosure kind of as Laura was speaking about, but I have received some research funding from a grant from CURE Epilepsy for a project about this topic specifically that was titled Jeavons Syndrome Improving Diagnosis and Treatment through a Modified Delphi Consensus Process. And I'll discuss some of the results we obtained from this today as well. And so, things we'll talk about, we'll talk the clinical and EEG features of epilepsy with eyelid myoclonia. We'll try and differentiate this epilepsy syndrome from other epilepsy syndromes and talk about how it's different and how the outcome may be different. And then we'll also talk about the preferred treatments for epilepsy with eyelid myoclonia. And we'll do that through first discussing the clinical features, the EEG features as that's a very important part of this diagnosis, the treatment. And then at the end we'll talk about the results of our international modified Delphi consensus process.

So what is epilepsy with eyelid myoclonia? So epilepsy with eyelid myoclonia is a rare generalized epilepsy syndrome. It was first described in 1977 by Jeavons, and so it was known as Jeavons syndrome for a long time. And then the name evolved to eyelid myoclonia with or without absence seizures. And then over time, this epilepsy with eyelid myoclonia is the name that's been accepted and has been used in the International League Against Epilepsy classification of epilepsy syndromes. And it's a rare epilepsy syndrome only accounting for about 1.2 to 2.7% of cases of epilepsy. And given its rarity, there's some difficulty with making the diagnosis and a lot of patients are misdiagnosed. In terms of the classification of epilepsy syndromes, the International League Against Epilepsy published updated classifications in 2022, included epilepsy with eyelid myoclonia as a genetic generalized epilepsy syndrome that we can see here and a few different graphs that they had from their publications.

And what we can see is that this is an epilepsy syndrome that is distinct from the idiopathic generalized epilepsy syndromes that are listed here and are more common than epilepsy with eyelid myoclonia. And then in another paper from the same classifications, we see epilepsy with eyelid myoclonia falling here with more of an uncertain prognosis as compared to other epilepsy syndromes like childhood absence epilepsy. And these classification papers and making the appropriate epilepsy syndrome diagnosis is very important as it plays a role in prognosis, in treatment and in the comorbidities that we see in patients and will be very important as we move forward with the hopes of clinical trial enrollment and things like that. And so, today we'll talk about how we differentiate epilepsy with eyelid myoclonia from other epilepsy syndromes. And just a little side note here is that there's also this very rare epilepsy

syndrome that's been recognized and studied called Sunflower syndrome, where patients actually look up at the sun and usually wave their hands in front of their eyes and will have seizures that may look similar to the seizures seen with epilepsy, with eyelid myoclonia.

While there are some debate about whether this syndrome is similar to epilepsy with eyelid, myoclonia or not, in the International League Against Epilepsy classification papers, it was denoted or classified as a subgroup of epilepsy with eyelid myoclonia, just to mention that. And so, how do we diagnose epilepsy with eyelid myoclonia? Well, there's first of all this diagnostic triad. So three things that we really look for that helps us determine if this is epilepsy with eyelid myoclonia. And the first thing, which may not come as a surprise given the name of the epilepsy syndrome is eyelid myoclonia. And this eyelid myoclonia is this very intense jerking or twitching of the eyelids where the eyes and the head may actually roll back. And we'll look at some videos of this and talk about eyelid myoclonia a little more. And this can be associated with or without loss of awareness.

And if patients are losing awareness, then it's defined as being an absence seizure associated with the eyelid myoclonia. Therefore, this is considered to be in some ways an absence epilepsy. And then the other thing that we see is that these episodes of eyelid myoclonia, or even the abnormalities that we see on EEG start after someone closes their eyes. So by closing the eyes, especially in bright lights, eyelid myoclonia can be induced. And then patients frequently have photosensitivity and we'll talk about that more as well. And that can be photosensitivity where the seizures are more likely in bright lights or artificial lights. But then also that we can see abnormalities when patients are given photic stimulation on an EEG. And so, in terms of epilepsy with eyelid, myoclonia who presents with this rare epilepsy syndrome? Well, we define this as a childhood onset epilepsy syndrome, and the average age of diagnosis is six to eight years when their symptoms may start.

Although as we'll talk about the diagnosis may be delayed by a long time, but there's a range still all falling usually within childhood from 2 to 14 years that patients can first start having the seizures. We see that girls are more affected than boys with a female predominance of 2:1. And I said that this is a genetic generalized epilepsy syndrome. And so, we think genetics have a role and we'll talk about that more as well. But family history is common among patients, but it can be a diverse family history of different epilepsy syndromes and not just that epilepsy with eyelid myoclonia runs in the family. Intellectual ability in these children, especially before seizure onset is typically normal. And as I stated, there is usually a delayed diagnosis. So seizures are an important part of any epilepsy syndrome and that includes epilepsy with eyelid myoclonia.

And so, eyelid myoclonia is really the main seizure type and it's required for the diagnosis. A lot of times we can witness this on exam because these seizures can happen multiple times per day, but without eyelid myoclonia you can't make the diagnosis. But eyelid myoclonia itself isn't unique necessarily to epilepsy

with eyelid myoclonia and may be seen in some other epilepsy syndromes. So it's important to take everything into consideration when making a syndromic diagnosis for the appropriate epilepsy syndrome. But most patients have more seizure types than just the eyelid myoclonia. And so, they can have absence seizures and a lot of times that may go with the eyelid myoclonia, but they can have absence seizures without eyelid myoclonia. And then most patients have generalized tonic-clonic seizures at some point during their course of epilepsy, although typically these are infrequent in an individual patient. Although there's definitely a subgroup that may have more frequent generalized tonic-clonic seizures.

And we may also see seizures like myoclonic seizures where patients can have jerks of their extremities associated with abnormalities on EEG. So what is eyelid myoclonia? So it's like I said, rhythmic jerking of the eyelids where the eyes and the head may be rolling back during these episodes. A lot of times this occurs right after eye closure, typically in bright lights and it's brief lasting usually around six seconds or so, but can occur multiple times per day, hundreds of times per dad even, especially in patients who aren't being treated yet. And this eyelid myoclonia may not be recognized as a seizure type right away as it's not a typical seizure type you'd see in a movie or anything like that. And so, a lot of times patients aren't appropriately diagnosed as having eyelid myoclonia and it's frequently misdiagnosed as eye movements.

I've seen multiple patients who are first referred to an eye doctor in childhood because they think there's dry eyes or another problem with the eyes, the eyelid myoclonia can be mistaken for a behavior eye rolling or other kind of behavioral movements. And so, it can take some time before these patients are even seen by a neurologist. And sometimes it's not until they have a generalized tonic-clonic seizure that these are then recognized. And so, here's some videos of eyelid myoclonia. All these videos are used with permission from patients. And what you see in this patient here is that when she closes her eyes, she then has this fluttering and eyelid jerking where her eyes also roll back. This patient, I'll play the video one more time, also has myoclonic jerks of her extremities, which we can see sometimes associated with the eyelid myoclonia.

And so, that's one example there. And I'll go to my next video here. Let's see, there it is. And this patient you see, he closes his eyes and he'll close them again. And then you start to see the eyelids fluttering, the eyes rolling back, and this patient has some loss of awareness during this period of time. He stops speaking to someone and loses track of thought there. And so, that's eyelid myoclonia. A lot of times we'll see abnormalities on EEG during this, but as the course of eyelid myoclonia goes on, sometimes we see the eyelid movements without changes on EEG as well. And certain triggers have been identified. And photo stimulation, like I said, as photosensitivity is part of the triad for the diagnosis. And then eye closure is when we a lot of times see the onset of the eyelid myoclonia changes on EEG.

And it's not only thought that maybe it's just eye closure itself that causes the seizures, but it may actually be elimination of central fixation of the eyes, which can be artificially done with different lenses and things like that. There's some debate in the literature about this though. And then as in with many epilepsy syndrome, stress or sleep deprivation can provoke seizures in these patients. There's been some reports of self-induction where it could be from such as with the Sunflower syndrome, where they look up at the sun and wave their hands in front of their eyes with the seizures. But this is another area of debate as such as in Sunflower syndrome, it's felt that that may be part of the semiology or part of the seizure itself. And so, I think this is still an area that requires further research. And so, how do we make the diagnosis of epilepsy with eyelid myoclonia?

Well, the clinical history is very important. So a lot of times patients', families or the patient themselves, they can think back and say, "Oh, these eye movements have been present for a long time. We just thought it was their normal behavior if it goes unrecognized." The neurologic examination is very important as well. The neurologic examination is typically normal with the exception that typically eyelid myoclonia can be witnessed in the exam room, especially if we shine a bright light in the eyes and have them close their eyes purposefully. And then an EEG is the other big part to make the diagnosis as we need to see the abnormalities that fits with the diagnosis on EEG. And so, we'll talk a little bit about the EEG here, but not in too many details. But typically, when we look at the EEG, this slide is talking about the EEG interictal or in between seizures.

And there's a typical background frequency in EEGs. And the background frequency is typically normal in patients with epilepsy, with eyelid myoclonia. But we can see that the EEG itself, the background activity looks very sharply contoured as opposed to a normal activity, especially after eye closure kind of fitting with the whole epilepsy syndrome. And then the changes we see on are EEG generalized changes. This is a generalized epilepsy. And so, we may see this generalized atypical spike in wave discharges and these abnormalities can be brought on by eye closure. And then when we use phodic stimulation with the flashing lights, photoparoxysmal response can be typically seen in these patients, especially if they're not currently being treated for their epilepsy. And then a lot of times in the EEG lab on a routine EEG, we'll also have patients hyperventilate and hyperventilation we know can induce seizures, especially in epilepsy syndromes like childhood absence epilepsy. But we also see that in up to 50 to 60% of patients with epilepsy, with eyelid myoclonia, this may provoke seizures.

And then when we look at the EEG during seizures and we call something ictal, so during the seizure EEG, and we consider the eyelid myoclonia to be a seizure. So during the eyelid myoclonia, we still see the generalized discharges on the EEG. Like I said, a lot of those times this can be induced by eye closure. And since patients can have such frequent events even in a 45-minute to a 60-minute EEG, it's not uncommon that we can capture some of these eyelid

myoclonic events on the routine EEG, especially when we have them close their eyes and when we use the photo stimulation.

And so, the photoparoxysmal response is when we're giving the flashing lights to patients during the EEG and we can see abnormalities on the EEG, there's extra electricity on the EEG associated with the increased risk of seizures. And like I said, photosensitivity is required for the diagnosis, but we know that photosensitivity in itself decreases with age and decreases with patients who are on anti-seizure medications. And so, having the lack of abnormalities during photo stimulation does not completely rule out this diagnosis, especially in patients on medication. The literature has shown that certain flash frequencies may be the most activating, and a lot of times we can see the eyelid myoclonia, if we look closely at the video during the flashing lights. And it's not just in the lab that this makes a difference, although it helps make the diagnosis.

But it's really that these patients notice this photosensitivity in everyday life and will have trouble with their seizures when out in the light, in the sunlight around artificial lights. And so, a lot of times if you just talk to patients, they're noticing this photosensitivity in everyday life. All right, and I just have some screenshots of EEGs just to try and show that these abnormalities from patient to patient once we start seeing these EEGs look quite similar for all the patients who have epilepsy with eyelid myoclonia. But on the EEG itself, this area of the EEG here looks pretty normal. The patient's eyes are open. This deflection here is actually artifacts from eye closure. So we can tell by looking at the EEG when someone closes their eyes. And a lot of times after we close eyes, we see more background activity in the back of the head, which is these leads here. And in patients with epilepsy, with eyelid myoclonia, we see that this activity here is sharper than we would typically see that arrow there points again to the eye closure.

And here's more examples from different patients as well where we have eye closure and then more sharply contoured activity than we typically see. And then we can see these generalized discharges in between seizures. And so, here's generalized poly spike and wave during sleep in a patient and we see that this is generalized as in it's showing that most of the brain is involved during this activity. And then here's some examples of actually what the EEG may look like during eyelid myoclonia, where again, the deflection seen on all these leads here is eye closure. So we see the patient closes their eyes and then over about three seconds because these lines here are one second, so of over three seconds, this patient has abnormal discharges. And actually when we looked at the video, had the eye movements associated with it, and we can even see some artifact in the area where the leads are closest to the eyes associated with eyelid myoclonia.

The patient then later has an eye closure here, which doesn't have any abnormal activity, but then you see later in the page just a few seconds later, again, eye closure with this brief episode of eyelid myoclonia. And here's just further examples of what sometimes we see on the EEG. These green bars are

one second apart. So again, it shows you that this can be very brief activity. This lasting just about a second and a half, and this is a longer episode of eyelid myoclonia, but again, after eye closure and then we see abnormal discharges throughout the whole brain. And then this is the EEG during the photic stimulation when we're doing the flashing lights, the lines at the bottom show us how fast the flashing lights are going actually. And we see that during the flashing lights there's this generalized very sharply contoured activity throughout the whole brain. So generalized kind of atypical poly spike and wave discharges associated with the flashing lights.

This is another example of during phodic stimulation and sometimes we see that it's not just that very sharp spike in wave activity, but it can be sharply contoured generalized activity at about the flash frequency that's given during phodic stimulation. There's been some data out there and studies looking at the photo paroxysmal response specifically. And then, let's see. Oh, sorry, it lagged. And apologies here, I'm trying to get this video to play. I am not sure if it will play for us. Oh, it looks like you got it to play. Okay, sounds good. So this is the video I showed earlier. So when the patient closes his eyes, we can see the eye closure on the EEG and on the video. And then you see that the EEG looks very abnormal where there's just a lot of generalized sharp activity. And so, you can see that there's this abnormal EEG change that fits with the eyelid myoclonia in this patient. I thought this was a nice example of what we're typically looking for on the EEG.

Okay, let's see here. And so, a lot of times when we diagnose epilepsy, brain imaging is a part of that. For the generalized epilepsy syndromes, the brain imaging is typically normal. And that's the same thing for epilepsy with eyelid myoclonia, we think that the brain imaging is usually normal or if it shows anything, it's mild or non-specific changes that would be unrelated to the epilepsy. And actually in the International League Against Epilepsy on classification papers, they said that an MRI is not required for the diagnosis of epilepsy with eyelid myoclonia. And then I said this is a genetic generalized epilepsy. So what about the genetics? What's the genetic cause of this? And like I said before, there's a high rate of a positive family history, although that positive family history can be unique. So there may be siblings that even have juvenile myoclonic epilepsy or other generalized epilepsy syndromes, but there are cases of epilepsy with eyelid myoclonia in twins as well suggesting this genetic predisposition or genetic cause.

But despite what we know that we think this has an underlying genetic driver cause, genetic mutations are only rarely found in patients. And really over the past few years there's been a couple more publications about this and listed here are some of the genes associated with epilepsy, with eyelid myoclonia. And when a genetic mutation is found, it's usually maybe associated with more likely to have hard to control epilepsy or intellectual disability as well. I think that genetics is an area that will grow rapidly, I'm hoping in the years to come and we should understand further the role genetics has in this and there may be further discovered in the future. And then what about comorbidities for these

patients? So with any epilepsy syndrome, it's not just seizures itself, but there's a lot of comorbidities we need to talk to patients about and think about.

I said development is usually normal, especially before seizure onset. There's a subgroup of patients who may have intellectual disability or school difficulties usually in the mild severity range. But we will see that the eyelid myoclonia, especially if patients are losing awareness, may result in school difficulties or we can't ignore the fact that all of our anti-seizure medications have the potential for side effects and potential for leading to further school difficulties. And so, this is still a problem for many of our patients with epilepsy, with eyelid myoclonia and like many epilepsy syndromes and epilepsy in general, anxiety and depression may be present as well. And so, it's something to screen for and to talk to our patients about it as well. And the rates of anxiety and depression and epilepsy with eyelid myoclonia itself is not well described in the literature, but I think it's likely quite high associated with the epilepsy diagnosis and everything.

So making the appropriate diagnosis is very important so that we can tell a patient, this is what your diagnosis is, this is what we know about the natural history of this epilepsy syndrome. This is the best way to treat it. But unfortunately for epilepsy with eyelid myoclonia, we know that diagnosis may be delayed by many years. And we know that many patients may be misdiagnosed as this eyelid myoclonia is not recognized as a seizure type by many. And so, how delayed could the diagnosis be? So this data right here is from a study I published in 2018 of 30 patients and in 30 patients, the diagnosis was delayed by an average of 9.6 years. So that's a long time for a person not to have the appropriate diagnosis. And as I am sure you can imagine then although this is a childhood onset epilepsy, we may be seeing patients that are first being diagnosed appropriately in the adult epilepsy clinic if there's such a delay in diagnosis.

And I said many may be misdiagnosed. And so, in a study by Ifrah Zawar, who's at University of Virginia, and she did this work while she was at Cleveland Clinic and she helped us a lot with the modified Delphi process over the last year and a half, she did this study of patients with epilepsy, with eyelid myoclonia. And from their group, they reported that 77% of first had a misdiagnosis, the incorrect diagnosis, and that was most frequently childhood absence epilepsy or juvenile myoclonic epilepsy. And so, I still think there's a lot of room for improvement in a faster diagnosis and an appropriate diagnosis. And so, when we have patients who come, who could possibly have epilepsy with eyelid, myoclonia, what other diagnoses are we thinking about? And that's other epilepsy syndromes and most commonly the childhood absence epilepsy and juvenile myoclonic epilepsy. And then we have to think about could these be ticks or behavioral eye fluttering and things like that. In these settings, you wouldn't have an abnormal EEG. So this is another area where the EEG can be very helpful.

And we put this table together for a publication about epilepsy with eyelid myoclonia comparing and contrasting it to two other common epilepsy syndromes, so childhood absence epilepsy and juvenile myoclonic epilepsy. And we can see that especially with the top two, they're both childhood onset epilepsies, but there are differences in the length of the absence seizures and obviously the eyelid myoclonia is mostly as associated with the epilepsy, with eyelid myoclonia, we can see some differences on EEG that help us differentiate it. And the reason it's important to differentiate it is because we know that the outcome is quite different between childhood absence epilepsy and epilepsy with eyelid myoclonia. And especially as the hope to have more specific treatments for epilepsy syndromes, we really need to appropriately diagnose patients with the right syndrome.

And so, how do we treat epilepsy with eyelid myoclonia? Well, the answer is mostly broad spectrum anti-seizure medications, which includes things like valproic acid, levetiracetam, lamotrigine, and other benzodiazepines. So anti-seizure kind of medications that work for generalized epilepsies. There are some anti-seizure medications that can make some generalized epilepsies worse, including epilepsy with eyelid myoclonia. And so, that could be sodium channel blocking medications. And so, if the patient doesn't get the appropriate diagnosis and they get placed on one of these medications, could actually worsen seizure control. That's kind of the main way we treat patients.

There is a special kind of lens therapy because as we talked about, a lot of times patients have this photosensitivity to bright lights and so there's a special lens therapy called the blue lens Z1 that's been studied for photo sensitive epilepsy and it's been shown to reduce photosensitivity. Unfortunately, it's not readily available. It can be difficult to get in the United States. And also, it really kind of makes the world dark and blue. And so, it can be very difficult also for patients to tolerate if they are able to get access to the lens therapy. And then in terms of we've had some new anti-seizure medications over the last several years and there's a growth in areas to treat epilepsy other than medicines such as neuromodulation like vagus nerve stimulation, responsive neurostimulators and deep brain stimulation. But given the rarity of this epilepsy syndrome, there's just not much published or known about the use of these treatments for epilepsy with eyelid myoclonia.

There's also dietary therapy, but again, there's just not much literature out there about how to use these in epilepsy with eyelid myoclonia. In terms of the outcome, from what we know from the literature, we know that patients may have drug resistance where their seizures may continue despite trying more than one anti-seizure medications. And especially the eyelid myoclonia may be difficult to control while the generalized tonic-clonic seizures may be easier to control with anti-seizure medications. And then we generally think of this as being an epilepsy syndrome, although it starts in childhood that patients are unlikely to outgrow and that they probably require anti-seizure medications lifelong. That's kind of what we know in the literature about outcome for now. But there's many unanswered questions in the literature about epilepsy with

eyelid myoclonia since it's rare, since it's underdiagnosed and since there's frequently a delay in diagnosis. And these many unanswered questions led to the project working with CURE Epilepsy over the past year and a half or so because what I've summarized so far is pretty much what we know in the literature about epilepsy with eyelid myoclonia.

And so, that's what sparked this project that we had called Javan syndrome or epilepsy with eyelid myoclonia and proving diagnosis and treatment through a modified Delphi consensus process. So the goals of this project were to try and establish standards to make an early and accurate diagnosis for patients so they don't have that diagnostic delay by almost 10 years. So we can educate people about distinguishing factors from other epilepsy syndromes, from other photosensitive epilepsies. We can see what people throughout the world think are the optimal therapies to treat seizures in these patients. We can try and characterize and understand the important comorbidities that come with this epilepsy syndrome. And so, we could provide some recommendations for the evaluation, what workup to do, who should get genetic testing, things like that, and the management and the treatment for both children and adults with epilepsy, with eyelid myoclonia, with the hope that in the future we'll be able to recognize these patients and maximize the potential for clinical trial involvement, especially as we're moving towards more epilepsy syndrome specific treatments and understanding genetics better.

But first, we really need to characterize things appropriately. And so, we use this modified Delphi methodology for this project that we started now almost two years ago. So this Delphi methodology was first developed in the 1950s by the Rand Corporation, and it's this rigorous consenting defining methodology that has actually been utilized in multiple areas of healthcare. There's some good examples in the literature to work off of including in multiple areas related to epilepsy. So Dravet syndrome, diagnosis and management, there's been both a North American consensus and an international consensus. It's been used in other things like epilepsy syndrome, definitions and then selection of epilepsy surgery candidates. And so, how does this process work that we worked on over the past year? And so, first we identified a steering committee with international representation with the help of CURE Epilepsy. This steering committee was our small working group of experts in epilepsy with eyelid myoclonia.

It involved physicians and patients and caregivers. So we had input from them about what's important. This group came together. We split out the important topic areas of epilepsy with eyelid myoclonia, and we went to the literature to summarize what was currently known, a lot of which I've already summarized in the earlier slides. And then we also worked to identify a larger group of experts, an international expert panel. We actually nominated people and voted and we wanted international representation. And then from there, we sent out our literature review to everyone on the international expert panel. And the steering committee also participated in three rounds of surveys, and each survey built on the prior results that we had received. For areas where the

literature is pretty clear that this is consensus, this is known about the epilepsy syndrome. We made statements and asked for strongly agree, agree, neutral, disagree, or strongly disagree.

We define consensus because I'll talk a little bit about consensus as strong if 80% of physicians agreed or moderate, if 67% agreed. And then we took all of the results, we summarized them, we tried to put things together in tables and in a format that could be helpful for kind of advancing this diagnosis and management of this diagnosis forward. And so who participated in our modified Delphi process? And so, this table here shows that in total we had 25 participants. We had mostly physicians seeing children, and then we had some seeing both adults and children. It was 25 and then we had patient and caregivers as well, which were five in total. And then at the first survey, we asked both the physicians and the patient and caregivers how comfortable they felt with different areas associated with epilepsy, with eyelid myoclonia. And just I want to draw everyone's attention to the fact that physicians felt pretty comfortable with things like anti-seizure medications, genetic testing, EEG imaging and clinical presentation.

But there was just less knowledge about things like driving neuromodulation and dietary therapies. And our results reflected that with areas where we could determine consensus. And so, from the results of this, we put together this table about trying to evaluate patients who present, where we suspect a diagnosis of epilepsy with eyelid myoclonia. And there is consensus for many areas. I've already kind of summarized a childhood onset of epilepsy with a female predominance, typically a normal development and frequent eyelid myoclonia, and they may also have other seizure types. We identified red flags being if patients had a severe intellectual disability or if they had other seizure types that we don't typically associate with epilepsy with eyelid myoclonia, such as atonic or focal seizures. And if the clinical history and exam supported epilepsy with eyelid myoclonia to further evaluate mostly with an EEG, a lot of times a routine EEG may be adequate.

And we had consensus for these abnormalities that we typically see on the EEG that we already kind of talked about, but that if there was background slowing or focal abnormalities on the EEG, that should be a red flag to consider an alternate diagnosis. In MRI, there was agreement among our group, the MRI was not required for a diagnosis, but if done should be normal or show non-specific changes and that an abnormal MRI with a causative lesion, which may be something in the back of the head, an occipital lesion should cause someone to reconsider the diagnosis. And then genetic testing, we asked our panelists about genetic testing and as I said, this was an international panel and so, there was a varying availability of different genetics. And so, not everyone had the same access to genetic testing. And so, we had asked the panelists if every patient with epilepsy with eyelid myoclonia should have genetic testing and we did not have consensus for that.

But there was a consensus to either get an epilepsy gene panel or whole exome sequencing when one or a combination of factors was present, which was a family history, intellectual disability or drug-resistant epilepsy. And then for treatment, one I think interesting area that we asked about was the goals of treatment. So I said, eyelid myoclonia can happen every day, it can be hard to control with anti-seizure medications. And there was a strong consensus from physicians and agreement from patients and caregivers that goals of treating the epilepsy syndrome would allow for accepting eyelid myoclonia as long as the other seizures are under control. And that's taking into consideration a balance between anti-seizure medications and the eyelid myoclonia itself. And then we ask about multiple different anti-seizure medications and there was a strong consensus for valproic acid, levetiracetam and lamotrigine of first-line treatment with ethosuximide and clobazam for second-line treatment. And then there was just less knowledge about some of the other medications. So we had no other areas of anti-seizure medications that had consensus.

But we did have a consensus to avoid sodium channel blocking medications except for lamotrigine, which does have some sodium channel blocking properties. And then from our publications and our results from this, we put together multiple of these tables. I won't read everything on this table because that's kind of burdensome, but we'll reference our publications at the end if people are interested. But I wanted to draw some attention to this topic, which is driving. So I said a lot of these patients have normal intellectual ability and driving is so important for independence, especially in different areas in the United States where public transportation is not as available. And so, we asked physicians if patients have uncontrolled eyelid myoclonia, but they're not losing awareness, should they be advised to not drive? And there was no consensus, which was kind of interesting.

But what we did get consensus for was that the physicians rely on the EEG to make recommendations about driving. And there's no great guidelines or consensus out there in how to use the EEG to make recommendations. But we asked physicians, go back here, multiple scenarios, "Would you allow this patient to drive or not based on these changes on the EEG?" And there were some variable responses with just few areas of moderate consensus. So even a normal routine interictal EEG. So I think this is another area that requires further research and understanding of whether at what point it's safe for these patients to drive, a balance between safety and independence. And then we also had multiple questions about outcome information. That did not go to the right place. Oh, these bars look a little off. I'm not sure what happened. I apologize for that. But there was a few things I thought were interesting.

And so, the first thing was that some patients actually may have a mild course that may never require anti-seizure medications, and there was a moderate consensus for that, which was interesting. When we had our publication in 2018 of 30 patients, we had one patient who had a mild course that actually came off anti-seizure medications because the side effects were worse than the eyelid myoclonia. We did have a consensus that seizures are likely to persist into

adulthood for patients, and that remission happens in less than 50% of patients. And then other interesting areas to highlight were that some things may be more associated with drug resistant epilepsy, like early age of onset or intellectual disability. And I think we need more understanding to understand if these are the patients who are more likely to have a genetic mutation. But there has been some publications that support this in the recent years.

And then there was also a consensus about there being two phenotypes. So two different groups of patients with epilepsy with eyelid myoclonia, one with an earlier onset higher proportion of intellectual disability and drug resistance, and one with a later onset normal intellectual ability and more drug responsiveness. And just a few kind of patient and caregiver-specific areas. So stress and sleep deprivation were noticed that it triggers in all the patients and caregivers who responded. And I think it was also important to highlight that all patient and caregivers thought that uncontrolled eyelid myoclonia can impact both social and psychological aspects of a person's life and can also be associated with bullying in the school and the work setting. So I think even though there was a consensus to allow eyelid myoclonia, I think we need better treatments for the eyelid myoclonia, because even if the seizures are not impairing awareness, they're still interfering with a patient's lives in significant ways.

And just a few highlights of some of the publications from this work with our group over the past year, we published the review we had put together in epilepsy research, and then the modified Delphi process was recently published in two publications in epilepsy, which can be seen here that summarize all of the results in much more detail. And then CURE Epilepsy has been taking the next steps to really advance patient advocacy. There's currently no patient group for epilepsy with eyelid myoclonia. I know they've been doing focus groups with patients and trying to build a patient advocacy community, which I think would be great to move things forward for this diagnosis and management. And then we submitted things to conferences and doing different educational initiatives, have this now on the NORD website to try and advance awareness about epilepsy with eyelid myoclonia.

And so, in conclusion, epilepsy with eyelid myoclonia is a rare generalized epilepsy syndrome, but the diagnosis is frequently delayed or misdiagnosed. Epilepsy with eyelid myoclonia has a triad or three things we look for, which is the eyelid myoclonia, that the eye closure itself induces the seizures or the changes on the EEG and then the photosensitivity. And typically we can diagnose this if it's recognized, if we focus on the history and a routine EEG and that eyelid myoclonia itself maybe drug resistant and we need better treatments. And really our modified Delphi process found multiple areas of consensus, but also multiple areas where we may not know the best management choices and where if patients are likely to be drug resistant, even if we say these are the best meds to use, they may not be working.

And so, really further work is needed in this area to advance the management of this diagnosis forward. And I just want to give a huge thank you to CURE

Epilepsy, especially to Laura who I've worked with closely over the past a year and a half or so. And then also to Dr. Wirrell, who's here at Mayo Clinic that helped a lot with this modified Delphi process. And then to everyone listed here who was on our steering committee, who had significant input for the work we've worked on and also want to thank our expert panel as well, that helped us put all these results together, and my references and then that's what I had.

Dr. Laura Lubbers: Terrific. Thank you so much, Dr. Smith, that was really informative. Really appreciate you describing that important work. So we'll now begin the Q&A portion. We have seven or eight minutes to address questions. So if you want to submit a question, please feel free to put it into the Q&A tab and click send. I already have a list of questions here we can start working on, and we'll do our best to get through them and perhaps Dr. Smith can address them offline, if we're not able to get to them all. So we've talked about the difficulty of controlling seizures in this epilepsy syndrome. Since it is hard to treat, what level of control should be expected and how do we know when to consider a new or an additional treatment or medication?

Dr. Kelsey Smith: I think that that's a great question and it's a question that I think should be very individualized and depends on the patient itself. So it depends on what a patient's goals are. If the patient really wants to be driving, then we need to try to escalate therapy to the point where the patient isn't losing awareness where that could be safe and also a risk-benefit ratio of trying a new anti-seizure medication. And so, I try and just have a discussion with my patient to see and for us to agree on that difficult question.

Dr. Laura Lubbers: Okay. Does the VNS or DBS work for this syndrome?

Dr. Kelsey Smith: That's a great question. So there's limited data out there. In our series, we did have some patients who had VNS implanted from our 30 patients we published in 2018. I have personally seen some patients who've had some nice response to vagus nerve stimulation, but I would just say we don't have enough knowledge. Deep brain stimulation as well, there's even less knowledge on. There's actually one case report of responsive neurostimulation to the thalamus, which is similar to deep brain stimulation. Deep brain stimulation is advancing in areas of generalized epilepsy, but there's just not as much experience in generalized epilepsy. So that also includes epilepsy with eyelid myoclonia. It's definitely an area of research and we should know more in the coming years.

Dr. Laura Lubbers: Great, thank you. So it's perplexing about lamotrigine. In your talk, you talk about lamotrigine works and can be prescribed, but sodium channels as a rule are not prescribed. So can you explain that dichotomy since?

Dr. Kelsey Smith: Sure. I'll try. And this is not just for epilepsy with eyelid myoclonia where there's this dichotomy. So we know that lamotrigine works for some generalized epilepsy syndromes. We use it in multiple generalized epilepsy syndromes. It can make myoclonic seizures worse. There's some good data for that. And

there's some debate about the eyelid myoclonia being just myoclonus of the eyes. But also, we know works usually well for the generalized tonic-clonic seizures and these generalized epilepsy syndromes. And that's probably due to other properties than just the sodium channel blocking properties. And so, I think it's a bit of a balance. If a patient has a lot of extremity myoclonus, that's something to consider when starting the lamotrigine. But still typically, it's one of our go-to medicines for generalized epilepsies despite its sodium channel, part of its action being at the sodium channel.

Dr. Laura Lubbers: Okay, that's helpful. Certainly, you can understand more. And along the same lines in a way, there's a question. Have combinations of medications been trialed for effectiveness against DEM? This person has seen some better control during medication transitions when there may be multiple meds on board. Is there any evidence for that?

Dr. Kelsey Smith: There's no great evidence for that to, most of the studies looking at epilepsy with eyelid myoclonia are retrospective studies. And it can be hard when you look at some of that data for the confounding factors of multiple medications. It wouldn't surprise me if there is sometimes a combination that works better balancing the eyelid myoclonia and things like that. But we just don't have enough data to say, I would say. There's a couple of retrospective series that puts some of the combinations together, but that data is limited and half interpreted.

Dr. Laura Lubbers: So, there are some new medications available now. Is there any knowledge about how well Xcopri might work?

Dr. Kelsey Smith: That's a good question. There was a series published actually out of Mayo by one of our fellow, Shruti Agashe, looking at Xcopri or cenobamate in generalized epilepsies. And I believe there was one patient with epilepsy with eyelid myoclonia in that. So obviously very limited data. There are studies that are hoping, my understanding is to study cenobamate or Xcopri in generalized epilepsies, and we don't have the results from those in general. So I just don't think we have enough knowledge at this time.

Dr. Laura Lubbers: Okay, great. So we are running short on time. I do want to make some... That people have been asking about the availability of this video and our webinar. And yes, we will be sharing this webinar on our website. Please give us a few days to get it packaged for sharing via our website, but it will be available for future viewing. And there have been questions about the videos. The videos have been appreciated, and questions about whether or not these can be made publicly available. In this webinar, we will not be making them publicly available, but CURE Epilepsy is currently working on a video series that we can share with the public so that people can get a better understanding of what these look like in the clinical condition. So stay tuned for more. We're hoping to have that information available later this year, as well as more educational material available.

There are more questions, and again, hopefully, we can have Dr. Smith address those offline and we will post those along with the video content in our website. So with that, I do want to wrap up and I want to thank Dr. Smith for your wonderful presentation in educating us on this topic. I'd also like to thank our amazing audience who always has wonderful questions and highly engaged, and we appreciate that very much. It makes these great fun to be able to educate such an interested audience. If you have additional questions about the topic or wish to learn about any of the Cure Epilepsy research programs or webinars, please visit our website or you can email us at research@CUREepilepsy.org.

I also want to let you know that we will be releasing an announcement of our next webinar very soon. It will be held on October 26th, and it will focus on epilepsy surgery and how it can reduce the risk of Sudden Unexpected Death and Epilepsy or SUDEP and other causes of death in epilepsy. That webinar will be in recognition of SUDEP Action day, which also occurs in October. So with that, I'd like to wish everyone a happy and safe weekend. Thank you for joining us again today. Be well.