Neuromyelitis Optica Spectrum Disorder (NMOSD)

You can view this presentation at: youtu.be/2oEpc7wEzjA

Dr. Eoin P. Flanagan: [00:00:04] Well, hello everybody. My name is Eoin Flanagan and I'm a neurologist at the Mayo Clinic in Rochester Minnesota. It's my great pleasure to be able to talk to you today about neuromyelitis optica spectrum disorder. These are my financial disclosures and some of which will be relevant to some of the treatments will talk about for neuromyelitis optica spectrum disorder.

[00:00:31] When we think about demyelinating diseases of the central nervous system, what we mean by the demyelination is removal of that covering of the nerves, that insulation that the nerves have in our brain, our spinal cord, and optic nerve. There are three main diseases that we think about. The first we've recognized for many decades and even centuries and that's multiple sclerosis and all of its variations. But the other two are more recently discovered. Today I'm going to focus in on the neuromyelitis optica spectrum disorder, particularly that associated with the aquaporin-4 antibodies.

[00:01:12] The origins of neuromyelitis optica, it was initially described in 1894 by a person named Eugene Devic and for that reason it's been termed in the past and still some people term it as Devic's disease. This was a 45-year-old woman patient who had paralysis and blindness and the pathology showed involvement of the spinal cord and the optic nerve. The terms that we use nowadays for this disease include the term Devic's disease subsequent to that it was termed neuromyelitis optica and then in more recent times it's been termed in neuromyelitis optical spectrum disorder. The term myelitis which is part of the terminology means spinal cord inflammation. We know that this disease particularly affects the spinal cord and the optica part of it refers to optic neuritis and the neuro refers to it being a neurologic disease. But not all patients will have both myelitis and optica myelitis and therefore the term neuromyelitis optica spectrum disorder was used to note that some patients will only have myelitis and might have multiple episodes. Other patients will only have optica myelitis.

[00:02:28] Other patients can have brain involvement without involving this final quarter optic nerve but still have NMOSD. I think there's an interesting journey that we can talk about with the aquaporin-4 antibody positive NMOSD that's happened over the last 25 years or so. That began over here on the left of the slide with the recognition. Excuse me, I'll just go back there. That began with the recognition that we can see on the left of the slide in 1999. The clinical course of neuromyelitis optica is different than MS. This is a study by

Dr. Wingerchuck and colleagues at the Mayo Clinic. They highlighted particularly the longitude and extensive lesion that we see with neuromyelitis optica spectrum disorder.

[00:03:19] Subsequently, pathology studies showed that when you looked at the brains or the spinal cords of these patients that we would see antibody deposited on the tissue and we also saw something that's called complement, which is a marker of the immune system. Both of those seem to be deposited quite regularly in this condition. In 2004 and 2005 Dr. Vanda Lennon at the Mayo Clinic discovered the antibody to aquaporin-4 which is a water channel within the brain, and it's located on a particular type of brain cell called the astrocyte. What we think happens is that the antibody then binds to that astrocyte, and you get this secondary demyelination and this inflammation that affects the brain, the spinal cord, and the optic nerve.

[00:04:08] There were many studies after the discovery of this antibody looking in the laboratory to see what were the immune factors involved in causing disease with this condition. It was realized that the B cells which make your antibodies seem to be important, that the complement seemed to be important that interleukin 6 which is like the fuel for your antibody producing cells, was also important and then plasmablasts which are also an antibody producing type of cell.

[00:04:43] In 2015 and 2016 there was diagnostic criteria published for neuromyelitis optica spectrum disorder which was an international group that defined the disease and were able to give particular characteristics to the criteria. Then in 2019 and '20 we really had the breakthroughs of treatments to prevent attacks of this disease and that included medication that targets CD19, it's called inebilizumab. A medication that targets CD20 called rituximab, and medication that targets complement called eculizumab and a medication that targets interleukin 6 called satralizumab. These were randomized controlled trials that really proved that these medications can be helpful in preventing future relapses and we'll discuss that a little bit later. But I think this gives you the overview of going from what the disease was thought to be a type of multiple sclerosis to being its own disease, to discovering how it was caused and how we could treat it. It's been a real success story in terms of how we've been able to develop treatments for the disease and very beneficial to all the patients out there with this disease.

[00:05:55] The disease is less common than multiple sclerosis, so it's a rare disease, about four per 100,000 in the United States people will have this disease. It seems to be a little bit higher in patients who are of African American or Afro-Caribbean ethnicity. Those patients seem to have the disease more frequently and also have worse outcomes, so there particularly we need to be very aggressive in treating those patients. There are other ethnicities that may be more predisposed, including Asian, Hispanic, Native American ethnicities may be at higher risk while Caucasians seem to be at lower risk, although that's different to MS where Caucasians are more affected.

[00:06:42] The epidemiology or the people that this affects, it tends to affect females for the most part much more commonly than males at a ratio of up 9:1 and the age of onset is typically around 30 to 40 years. Some patients will have connective tissue disorders so they might have lupus or Sjogren's syndrome, coexisting with neuromyelitis optica and even some patients can have other neurologic autoimmune diseases like myasthenia gravis.

[00:07:10] The main clinical features are three types of attacks that patients have with the neuromyelitis optica spectrum disorder. The first is called optic neuritis, which we can see here on the left where we see an MRI showing evidence of inflammation within the optic nerves. The second we can see is transverse myelitis which we can see here in the middle with this long area of signal abnormality. Then the third is an

area postrema syndrome which can result in nausea, vomiting and hiccups. Some of these patients initially present to a gastroenterologist and then are later told that they have the neuromyelitis optica. The optic neuritis can cause episodes of blindness in one or both eyes and the transverse myelitis tends to cause numbness and weakness in the legs to the point where patients can have difficulty with walking and also may have difficulty with bladder function and bowel function. So that's the main symptoms. The attacks with this condition tend to be more severe than with multiple sclerosis, so these patients often when they have an attack, they might require assistance to walk with a cane, a walker or maybe need a wheelchair or scooter during the attack. But the hope is that we can improve them from that attack and then prevent further attacks.

[00:08:32] There are other areas of the brain that can be involved. This picture on the right here just shows the areas that aquaporin-4 which is that water channel we talked about this antibody attacks and that shows the areas that it binds to. Those areas that are highly enriched in this aquaporin-4 are the areas that we can see involved on the brain MRI and we can see symptoms related to those as outlined here. Now the great thing about the NMOSD is that we have a very good blood test that we can make the diagnosis. In multiple sclerosis, we don't have a blood test that we can make the diagnosis and we have to use MRI and spinal fluid and put things all together. With this disease, we have a very reliable blood test and it's this antibody to the aquaporin-4. This is best tested in blood, so you don't want this to be tested in spinal fluid but actually it's a blood test that's the easiest and of course that's the best test for this. We use a certain type of technique called a cell-based assay technique which is what's recommended. There is another technique that we can detect it with called the ELISA assay but that has a risk of false positive results at low level, seem to be a little bit careful with low positive on the ELISA test and the cell-based assay is what is recommended.

[00:09:54] Now here we can see a picture of what happens when the antibody binds to this water channel and what you'll see here is that it can bind, and it can cause internalization or what's called endocytosis. It can also bind to the receptor and cause dysfunction. It can also bind and recruit in other immune cells that will attack the brain or the spinal cord or the optic nerve or it can activate this protein called complement that can lead to a cascade of additional inflammation and some of these areas are the areas that we target with our treatments.

[00:10:32] The clinical course of the aquaporin-4 which is in the middle here is a little bit different to the other diseases. What you'll see here in the middle, along the x-axis here what we see as time and on the y-axis, something called EDSS which is a measure of disability. What you see here is that with each line going up is a patient who develops increased disability with an attack and then what we can see is it comes back down to another level but each with each attack, a patient tends to get more disability. It's really important to prevent those attacks because after one attack the patient may require a cane, after two attacks, they may require a walker and after more attacks they may require even additional assistance to get around. Really, we have to be able to treat these attacks very aggressively and also get patients on the best treatment to prevent those attacks.

[00:11:30] Now, what about seronegative NMOSD? These are patients who have neuromyelitis optica spectrum disorder but are negative for the aquaporin-4 antibody. Well, there's one other antibody that can cause a similar syndrome and that's the MOG antibody. If you have a seronegative NMSOD you want to make sure that you are tested for a MOG antibody because that's a different disease and requires a different type of treatment and has a different outcome and different prognosis. I will give caution that seronegative NMOSD is a complicated, probably a group of disorders, some patients may have multiple sclerosis, some may have sarcoid and really if you have seronegative NMOSD you want to make sure that you're seen at an expert center or subspecialist opinion because those cases are complicated and sometimes, we can

tease out the correct diagnosis and get patients on the correct treatment. They're not as straightforward as the aquaporin-4 antibody positive cases where we know the best treatment. These require a little bit more extensive investigations to determine the exact cause.

[00:12:35] Now when we think of these attacks that happened with NMOSD, we generally treat them with high dose steroids. As many of you know that will involve having an IV placed and giving what we call one gram of IV methylprednisolone or Medrol which is a type of high dose steroids for five days. In fact, in recent times, we recognize that we can now give a high dose oral formulation that involves taking 25, 50 mg tablets every day for five days, but it works similarly and if people don't have any stomach issues it can be an alternative option to get treatment started right away. But what I will say is that really, we should have a very low threshold to use plasma exchange or plex. This is a treatment that removes all your antibodies. It's like a dialysis type machine that removes all the antibodies in your body including presumably those bad aquaporin-4 antibodies. It seems to be very effective for patients and the earlier the better. If I'm a patient with NMOSD I want to be telling my doctor that really pushing for this plasma exchange as soon as possible if I have a severe episode. If you just have some mild episode, mild blurring, mild numbness you may not need it, but I think the vast majority of patients should be getting this treatment and the earlier the better. Plasma exchange really pushed for that for those acute attacks because it really seems to help patients recover from those attacks.

[00:14:02] In terms of preventing attacks, there's a number of medications that are mentioned here and many of these are recently FDA approved in the United States. For example, if we take the first row eculizumab which is a medication that targets complement, it's given every two weeks, it is a very costly medication up to $700,000 per year but it's highly effective. There is one particular infection that we have to be careful about it and that's a meningococcal infection that can cause meningitis. In general, what we will do is we will give patients vaccinations for that before they start the treatment, and we sometimes even have to give them regular daily antibiotics to prevent the risk of that type of infection. Eculizumab again a very effective medication, inebilizumab another very effective medication is also FDA approved has been performed in that placebo controlled randomized trial. This treatment targets the CD19 which is a marker on B cells and plasmablasts that make your antibodies.

[00:15:07] Again, we talked about the plasma exchange in the acute attacks, removing all your antibodies, this is preventing the antibody production so it's another way of preventing those bad aquaporin-4 antibodies theoretically from being produced. This is every six-month medication, again, it's quite a high cost, up to $300,000 per year, so quite an expensive medication. What it does, it can reduce your antibody total antibody level so we usually have to follow that over time because all of these medications will increase your risk of infection. The third medication I'd like to mention on the list here is the satralizumab that's also FDA approved and that targets the IL-6 receptor which the way I think about the Interleukin 6 is it's like a fuel for your B cells. It helps your B cells in your plasmablasts to make those antibodies. We are now targeting the fuel for the B cells rather than the B cells directly to prevent them from making this bad antibody. Again, the cost of this medication is quite high. But it's FDA approved and often insurance companies will approve these medications because they are proven to work and are highly effective. This medication is a subcutaneous medication and there are certain side effects that can occur as mentioned here including a risk of infection of course, with all of these medications.

[00:16:31] The fourth medication here is rituximab that is a treatment that targets the CD20 which again is located on B cells. Again, it's in every six-month infusion similar to the inebilizumab above and it's a little bit less costly and there are biosimilars available and it if cost is an issue of insurance approval is an issue, this medication can be an option. It does reduce that antibody levels, so that's also an issue and it can reduce the response to vaccination about that and the inebilizumab as we mentioned earlier. It does have class

one evidence to support it in a small clinical trial. These four medications are really some of the main states that we will use. Another option is to tocilizumab which is not FDA approved and will be off-label but targets the IL-6 receptor similar to the satralizumab. Then the older generation medication mycophenolate and azathioprine have been used are oral medications. They are a little bit problematic in that they haven't been proven in these clinical trials and also when you use them for a long time, there's an increased risk of blood cell cancers and they take a long time to work 3-6 months. Many patients need to be on cortical steroids with a lot of side effects for that six-month time period. They're a little bit more problematic but they are more affordable. If there are cost issues, they can be good options and they do work well for the disease. But we don't have as much proven data as we have for the top four options mentioned in the table here.

[00:18:16] There are other treatments that we will do for NMOSD, sometimes patients can get spasms in their arm or leg where their arm will flex up lasting about a minute at a time and that's very responsive to medication called Carbamazepine. If you develop these spasms that come very painful sometimes precipitated by movement or increased breathing, that can be helpful. We can use medications like baclofen and tizanidine for muscle stiffness or spasticity. We have medications that can help with bowel and bladder function. If patients have that nausea, vomiting and hiccups that we mentioned earlier, sometimes IV fluids and anti-nausea medications can be given. Then a lot of patients unfortunately leftover nerve pain and we try to treat those with oral medications like duloxetine, gabapentin or pregabalin.

[00:19:05] Other non-medication approaches sometimes in patients who have low vision we have a system device and there are low vision clinics that can help you with different instruments that can help there including iPad related things also or device related help bladder care. Some patients will require intermittent or regular prolonged catheterization so that there can be helped with that from our neurology colleagues. We will sometimes have our patients go to see physical therapy and occupational therapy to rehab their muscles. Then sometimes patients will need an assistant device like a cane or walker as outlined here and then we have non medication options for pain management that are outlined here. Exercise is also going to be very beneficial and sometimes a recumbent bike can be used if patients have imbalance, so that could be an option. In some patients very severe involvement in the upper spinal cord can affect their breathing and sometimes we'll have to temporarily give them breathing help with machines like a BiPap or a ventilator machine temporarily while we treat their attack.

[00:20:16] I'd like to conclude there by just saying that NMOSD is a potentially severe disease that affects mostly the optic nerve and spinal cord. We now have very effective treatment, so this is a really hopeful time for our patients both to treat the acute attacks and resolve the symptoms from those and to prevent future attacks. You really want to be thinking about this plasma exchange treatment and then one of the treatments to prevent future attacks. I will say that there's a lot of hope out there for NMOSD patients, back 20 years ago we didn't have as many treatments available, and patients tended to have a real hard time and a lot of disability and shortening of life was happening in our patients. Now with these new medications I think the future is much brighter, once patients can get onto an effective medication, we can really keep the disease quiet for the future. I'd like to thank you all for your attention and I'll look forward to taking any questions.