Acute Treatments at Onset and Relapse

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[00:00:00] **Roberta Pesce:** Our next talk is such an important talk. We say this often at SRNA, it is extremely important to begin treatments as soon as possible after a rare neuroimmune diagnosis and following a relapse. I'm joined now by neurologist, Dr. Flanagan from Mayo Clinic, who will tell you a little bit more about the acute treatments that are used to quiet down the immune system after an attack. Dr. Flanagan, welcome, and over to you.

[00:00:30] **Dr. Eoin Flanagan:** Great. Thanks very much for the opportunity to talk to everyone today. Today my talk is going to be on acute treatments at onset and at relapse. So, these are my disclosures, which are not really too relevant to this talk which is going to talk on acute treatments. So, the learning objectives today are to highlight the importance of early, as was mentioned earlier, and effective acute immune treatments in CNS demyelinating disease, and I'll also highlight a little bit about other medication and non-medication treatments that we use in the acute setting when patients come in with attacks of these diseases. So, I'm going to start off with a case.

[00:01:12] This is a patient that I saw at the Mayo Clinic in the Neuro ICU back in 2015. He was a 47-year-old man, and he had presented initially with a flu-like illness feeling unwell, and then he developed some confusion and numbness and weakness in his arms and legs. And this progressed, and he also began having difficulty emptying the bladder. And also, some breathing difficulty and swallow troubles. And this was happening over the course of a couple of weeks, and then the patient progressed to a more severe state, where he became in a coma and was completely paralyzed in his arms and legs. So, this was a pretty significant episode for this patient, and he required a breathing tube, as I'll talk about later.

[00:01:55] At the time he was evaluated with an MRI, and we can see the MRI here showing these multiple white matter lesions, or areas of abnormality. And we can see here in the spinal cord some white area. That is also abnormal involving the spinal cord. We can also see here in the axial sections. And this patient underwent a spinal tap, as is often done in this situation to look for infections or cancer cells. We didn't find anything. And at the time actually a brain biopsy was done, which just both of those showed prominent inflammation. And actually, at the time we had the MOG antibody available here at Mayo Clinic just on a research basis, but we did send it off. It took a little bit to come back, but it came back strongly positive.

[00:02:39] So this patient had initially presented with a syndrome that we would call acute disseminated encephalomyelitis, or ADEM, and then when the MOG antibody came back positive we were able to change the diagnosis to a more specific diagnosis that we termed MOG Antibody Associated Disease. And this patient underwent immune treatment, so this is a good example of the types of treatments we might use. He was given IV steroids and plasma exchange, and then he was placed on some oral steroids, oral prednisone, for 2 months followed by a slow taper over a subsequent few months.

[00:03:12] And, in addition to the medication treatments, the immune treatments, this patient also required a lot of supportive care because he was in a coma and completely paralyzed. So, he had to be on a breathing machine for many days. He also required a feeding tube to ensure that he was fed during this time. His bladder was not working, so he required a urinary catheter, and also required a bowel regimen. And this patient, even from the earliest point when he was seen at Mayo Clinic when he was very sick, we involved occupational therapy and physical therapy, so that's an important component of the acute treatment. And the great thing was, was that this patient, after this treatment, came back to my office 3 months later and was pretty much back to normal. So, you can see that this patient went from as sick as a neurology patient can get back to normal. This shows you the power of some of these acute treatments that we use.

[00:04:03] So I'm just going to give a quick message here about how we think some of these antibody mediated disorders work. So, we know that there are antibodies to MOG and antibodies to something called aquaporin-4, which are things that are located on the surface of the cell within the brain. And what we think in these cases is that the antibody that the body has made against itself, which it's not supposed to do, is causing the problem. So, the antibody can bind to some of the receptors on the cell and then those receptors, like a water channel for example with the aquaporin-4 or the MOG receptor, and that makes the cell not work. And when that happens on a global level then patients will get symptoms.

[00:04:45] So what we think is when we target these patients acutely, that we can try and target the antibody, and one way of doing that would be to try and remove all the antibodies, which I'll talk about, with a treatment called plasma exchange. Another way to target this antibody would be to try and neutralize it with a treatment like IVIG. And then steroids are also a main type of immune treatment that we can dampen down some of this inflammation that we can see here. So, when we think about inflammatory demyelinating diseases of the central nervous system, it's important to think about the types of attacks that we have and the syndromes that we can have. So, this patient that I mentioned had something called ADEM, or acute disseminated encephalomyelitis.

[00:05:26] But other patients can have transverse myelitis, that can be from demyelinating disease, such as with MOG or aquaporin-4 antibodies, or it can be from infections or related to the enterovirus. I know many have talked on acute flaccid myelitis. Or sometimes we'll term it idiopathic, which means we don't know the cause. Other descriptions you'll hear of is optic neuritis, which means, the '-itis' in all of these means inflammation, so optic neuritis means inflation of the optic nerve. Encephalitis, inflammation of the brain. Brainstem encephalitis, involvement of the brainstem. And then sometimes if you have combination, you might have transverse myelitis and optic neuritis that we term neuromyelitis optica.

[00:06:06] And I think when we think about the demyelinating diseases in the brain, there are really three specific ones that we can parse out well at this time. One is multiple sclerosis, and the other two are associated with the aquaporin-4 antibody positive neuromyelitis optica spectrum disorder, or NMOSD, and myelin oligodendrocyte glycoprotein antibody associated disease. And really the acute treatments for all of these are quite similar, as I'll show. So, when we think about the immune treatments, we want to think about some principles.

[00:06:36] How do we treat these patients? So as was mentioned, the earlier the better with these treatments and that's important. And we often start with high dose steroids, and indeed there are some trials going on where people can have what we call a steroid in the pocket trial, where you would have an oral steroid at home and if you developed your symptoms on a Friday night, can't get in touch with your doctor, that that might be an opportunity and we're trying to see if that might be an effective way to treat some patients if they were to have a relapse at an inconvenient time. And we have a low threshold for additional treatments.

[00:07:09] You can see that the first patient that I mentioned earlier was very severely affected, so sometimes we'll even use those additional treatments concurrently with the steroids if it's a severe episode. So, the high dose steroids that we use are first line for demyelinating attacks, and this is often high dose IV steroids where it's given at an infusion center or when a patient is in the hospital. But we do now have alternatives, and we've been using these more in the setting of the pandemic because we haven't wanted to bring patients who are immunosuppressed sometimes into a medical facility where there could be a risk of transmission of infection.

[00:07:46] And in this situation it has been shown that high dose oral prednisone, which is 1,250 milligrams, quite a high dose, for 5 days can be quite equivalent to this IV steroids. And the benefit of that is in patients who live in rural communities or don't want to come into the hospital, this can be an acceptable alternative. The only problem is it involves taking 25 tablets every day for 5 days. So, you have to kind of take 25 over the course of an hour, which can be bit of a hassle, but it's also a hassle to go all the way into the hospital, particularly if you don't need to be in the hospital for other reasons if you don't need other hospitalized care. Sometimes we'll use oral steroids after an acute episode as a transitional treatment, so with MOG antibody disease for example, sometimes we'll use steroids for a few weeks or months to try and prevent an early relapse.

[00:08:36] And then with aquaporin-4 positive NMOSD, sometimes we'll use the steroids as a bridge while we're waiting to get insurance approval for those chronic maintenance treatments that we use in that condition. Just to remember that, as many of you are likely aware, that steroids do have side effects. So, they can cause insomnia, and in elderly people they can sometimes cause confusion. Sometimes they can interfere with blood sugar, which is important for patients with diabetes. They can also cause high blood pressure. And they often cause weight gain and puffiness, particularly around the face and the neck region, so that can also be a side effect, particularly when they're used more in the long-term. In the short-term there's not as many side effects and usually we can deal with them. In the longer-term or medium-term it's more of a problem.

[00:09:23] Just to mention about some other treatments, one way, as I said, of treating these is targeting the antibody. And the plasma exchange is like washing out all your antibodies. So, you have all these antibodies in your system, that some of which are causing a problem. So, one way to do this is to try and wash them all out, and then eventually come back, but that can help patients in the acute setting. And this is particular useful for the aquaporin-4 positive NMSOD. There's been a lot of studies suggesting how useful this is with attacks of that condition, so you really want to consider and have a low threshold for this treatment in the NMOSD patients. There can be side effects with this. Sometimes the blood can clot in the line.

[00:10:02] We can see this patient has a line in his arm. Other times we need to put the line into the neck, so sometimes as we place that line that can cause a problem or there can be a risk of puncturing the lungs. And sometimes patients can have cramps. But the first patient I mentioned did get this treatment and you can see, in combination with steroids, how much of a difference it made. So, it can be really an important treatment that we have available. And again, earlier treatment, the better. Intravenous immune globulin, or IVIG, is another treatment that we can give, and we give that through an IV in the periphery. We usually don't need a central line in the neck for that one. And this is less commonly used acutely, I would say. Sometimes it's used more chronically to prevent attacks also, such as with MOG antibody disease.

[00:10:50] And the side effects of this one, it works well, but sometimes people can get an allergic reaction, and we usually check for something called the IgA before we start using it. Sometimes patients can get a headache when they get the treatment, so sometimes we recommend that the nursing team slow down the infusion when they're there because that can cause a problem. The medication can be hard on the kidneys, particularly in people with kidney impairment, and sometimes if we remove the sugar component of that, that can help. And then sometimes it can increase the risk of blood clots, so we have to be careful if patients get a swollen leg or swollen arm after that treatment.

[00:11:28] Acute flaccid myelitis, we don't really have as many immune treatments. This is mostly supportive treatment in the acute setting. We have sometimes tried IVIG, and other providers have tried that. It's sometimes used, but steroids tend not to be used as much, and plasma exchange, and there's some concern about the potential that those could worsen things. So really acute flaccid myelitis is going to be more of your supportive treatment, which I'll talk through. There are other non-immune medications that sometimes we use. So sometimes patients can be bothered by nerve pain during their episodes, and it's reasonable to get started on nerve pain medications right away if patients are having difficulties. That would be medications like gabapentin or Neurontin, pregabalin or Lyrica, for example.

[00:12:11] Some patients, particularly with the aquaporin-4 antibody, can have tonic spasms, where they get these spasms that last about a minute or two and can be very painful for patients, and they tend to respond very well to a single medication called carbamazepine. Another name for that one is Tegretol. And even at a low dose that seems to be able to resolve those very painful and difficult symptoms that patients can get. Usually follows the attack. Usually, it's within the first few weeks after the attack. And then we know that with our aquaporin-4 antibody positive NMOSD patients, sometimes they can get nausea, vomiting or hiccups. That sometimes get mistaken for gastroenteritis, and sometimes we'll use nausea medications and other things, IV fluids, to help with that part.

[00:12:54] Finally, I will mention about supportive treatments. So, when you're in the hospital it's important for patients to be their own advocate because they're going to remember some of these things when sometimes the doctors can miss it. So, the doctors will usually pick up the breathing issues, so if there's acute breathing issues from, say, a myelitis or a brainstem syndrome, some of those muscles control your breathing and it's important to protect the breathing really early on. So sometimes patients need to be put on a breathing tube in this situation, usually temporarily until they can get improvement. Sometimes if they can't swallow it's important because we don't want patients to become malnourished, and therefore it's important to always remember about feeding. And sometimes patients can bring this up to us also, so it's important for patients to remember about that.

[00:13:37] And bladder care, sometimes we'll have to put a urinary catheter in. We don't like those to stay in too long because they can increase the risk of infection. So sometimes we try to get them in early on, and then once we get the patient treated, we try and remove it. Also preventing against constipation, some of the pain medication, like opioid medications and being immobile from some of these conditions can result in prominent constipation, so we usually try and get on top of that very early on. And then we want to get involvement of our physical and occupational therapists to help with the rehabilitation in this condition. And then also we want to manage and prevent complications, so oftentimes we'll use blood thinners to prevent against clotting in the legs. We'll try and turn the patient frequently to prevent against any pressure sores. And this is just mentioning here about the breathing issue, we recently did a study published in the Journal of Neurology where very rarely, but sometimes patients with attacks with the MOG antibody or the aquaporin-4 NMSOD condition can have respiratory failure and be required to have a breathing tube, so that's something also to be aware of.

[00:14:43] So I think I'm going to conclude there, and I'm going to open it up for questions. But I think the principles are treat early, and if steroids don't work look for additional treatment, such as this plasma exchange treatment, this PLEX, particularly with the aquaporin-4 antibody. You really want to be considering that in that condition. And then remember that there are other important treatments, both medication and non-medication treatments that are important in this condition to make sure we maintain nutrition, we prevent constipation, we prevent other complications.

[00:15:15] So I'd finally just like to say thank you to all the patients out there. I know many of you have gotten involved in research, and the way we learn from how to treat these conditions is by doing research. And I know all of you have given your time and everybody is so interested in the condition, so it's just a great pleasure to be able to help and kind of try and educate people about the important things that we think about.

[00:15:39] **Roberta Pesce:** Thank you so much, Dr. Flanagan. This was incredibly helpful. We have received some questions from our community. I'm going to pull them up right now.

[00:15:49] **Dr. Eoin Flanagan:** Okay.

[00:15:50] **Roberta Pesce:** The first one is, what determines if someone needs more than just steroids?

[00:15:55] **Dr. Eoin Flanagan:** So, I think one idea there would be if a patient is still pretty disabled. So, for example, if a patient just has some numbness and they take steroids, usually we would wait and see how that goes. But if a patient is very paralyzed, not able to walk, still blind in one eye or with severe vision loss after 5 days of steroids, then we really want to think about moving on to one of these other treatments because we know that some of those patients can end up blind in one eye or paralyzed in the long-term, so we really want to treat aggressively if they're not getting better with the steroids. Some of the conditions are quite responsive, like the MOG antibody. Even if a patient is very severely affected, they often rebound very quickly with the steroids. But with the aquaporin-4 NMOSD it's really important to consider these additional treatments early on.

[00:16:44] **Roberta Pesce:** Yes, yes. Great. Thank you. And we have another one that just came in. You mentioned symptomatic treatment of nausea, vomiting and hiccups for NMOSD patients. If that is a new symptom for them could that signal a new attack?

[00:16:58] **Dr. Eoin Flanagan:** Yeah. They're exactly right. So, there's an area in the brain that controls your vomiting called the area postrema. And in addition to the spinal cord and the optic nerve, that area postrema, for some reason, is predisposed to being involved with the NMOSD. So, a lot of times that does mean that they're having an attack. And actually, while we'll treat the nausea and give IV fluids, we often have to give those immune treatments, the steroids and the plasma exchange, to help with that. So, if you do have those symptoms and you have the NMOSD, you want to talk to your doctor about the possibility that it's not just a gastroenteritis and indeed it is a relapse of your condition.

[00:17:34] **Roberta Pesce:** Great, great. Thank you. We have quite some questions come in. I'm just going to keep going.

[00:17:39] **Dr. Eoin Flanagan:** Sure.

[00:17:40] **Roberta Pesce:** When steroids and PLEX didn't help I did cytoxan infusions for a year, and that cleared up the inflammation. I don't see that mentioned often. This is more of a comment.

[00:17:50] **Dr. Eoin Flanagan:** Yeah. Cyclophosphamide we sometimes use, particularly with multiple sclerosis. I didn't have time to cover all of the other treatments, but certainly if you have a very fulminant case, which means a very, very severe case, sometimes we will use cyclophosphamide as an additional immune treatment. So that's another one that you could certainly consider, usually in very severe cases because it's a chemotherapy. It has a good number of side effects, so we usually reserve that for really, really severe cases. But yes, that's correct, and it can work, like in this patient's case.

[00:18:23] **Roberta Pesce:** Great. And I think there's another one that is very interesting. Have you or your colleagues changed steroid protocol during the COVID pandemic at all out of immune suppression concerns?

[00:18:35] **Dr. Eoin Flanagan:** Not so much we've changed because a short course of steroids is not that immunosuppressive. It's not that risky to do that for 5 days. And actually, steroids are part of the treatment for COVID. We use dexamethasone for COVID-19 infection. So more what we've done is we've moved towards that oral treatment where we will give the patient the treatment in their house, so they wouldn't have to come into the medical facility. That's something that we've tried to do when possible and patients have been appreciative of that. So, I would say that's the major change. Otherwise, we haven't changed our practice that much with the acute treatment.

[00:19:08] **Roberta Pesce:** Great. Great. Well, thank you so much, Dr. Flanagan, for your time today. It was great hearing a little bit more about all of these options, and we appreciate your time.

[00:19:19] **Dr. Eoin Flanagan:** Thanks for the opportunity, and thanks to everyone at the SRNA and all the patients out there. I really appreciate them.