Acute Disseminated Encephalomyelitis (ADEM)

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Dr. Brenda Banwell: [00:00:05] Hello everyone, my name is Brenda Banwell. I am the Chief of Neurology and the Co-Director of the Neuroscience Center and Professor of Neurology and Pediatrics at the Children's Hospital of Philadelphia, University of Pennsylvania. It's my pleasure tonight to talk to you about acute disseminated encephalomyelitis.

[00:00:23] These are my disclosures. I serve as an advisor and consultant on clinical trial design and execution of clinical trials for pediatric patients. I am also the chair of the International Pediatric Multiple Sclerosis Study Group, and chair of the Medical and Scientific Advisory Board for the Multiple Sclerosis International Federation.

[00:00:44] So, the first attack of central nervous system demyelination in a child or adult can manifest in a variety of ways. Patients can present with optic neuritis, ON, as shown here with inflammation of the right optic nerve, with inflammation in the spinal cord or transverse myelitis, brain stem symptoms that may be a single location, referred to as a monoclonal clinically isolated syndrome, or on the far right can have multiple lesions as shown in this MRI scan. Everything that's bright white is an area of focal inflammation. And this was a young patient with their first attack of multiple sclerosis.

[00:01:26] But ADEM, as illustrated here on the far left of the screen, acute disseminated encephalomyelitis, I will call it ADEM from now on, also presents with multifocal white matter changes in the brain, can also include optic neuritis and, many children and adults with ADEM also have spinal cord inflammation. Any of these presentations can have a different outcome. So, patients with a first attack of demyelination may have a monophasic single event and no further disease, referred to here in purple as monophasic-acquired demyelination, can have the first attack of aquaporin-4-related neuromyelitis optica spectrum disease, or NMOSD. Not so commonly is that is a patient with ADEM likely to have aquaporin-4 antibodies.

[00:02:19] Patients can have myelin oligodendrocyte glycoprotein-associated disease or MOGAD, and patients with ADEM can definitely have MOG antibodies, and finally multiple sclerosis. ADEM, as a demyelinating event, is very, very infrequently the first attack of multiple sclerosis.

[00:02:44] So, what is ADEM? So, ADEM, and this definition is in the pediatric ADEM definition, but does also apply to adults. So, ADEM is a first clinical attack with a presumed inflammatory or demyelinating cause. Children and adults have an acute or sub-acute over the course of several days onset of symptoms and these symptoms affect multiple areas of the central nervous system, which leads to polysymptomatic presentations. A core requirement for the diagnosis of ADEM is that there must be encephalopathy. And encephalopathy itself is defined as a behavioral change, extreme irritability or profound lethargy, alteration in level of awareness and consciousness, somnolence and sometimes even coma. And about a third of children with ADEM will have seizures.

[00:03:39] Imaging features, which we will illustrate more on subsequent slides but are very characteristically demonstrated by focal and multifocal lesions involving the white matter, but also typically involving deep gray nuclei, can involve the cortex, definitely can involve the spinal cord and occasionally can involve the optic nerves. Relatively infrequently, patients with ADEM will have established areas of T1 hypo-intensity or black holes, which typically in the case of other demyelinating conditions are a late phenomenon after periods of prolonged inflammation. So, not surprisingly, black holes are not very characteristic of an acute presentation like ADEM.

[00:04:27] Most patients with ADEM will improve clinically and on MRI although some can have some residual deficits. For a patient manifesting with true first event ADEM, there should be no prior history of demyelinating events. And of course, like anything, we also want to rule out other causes of acute confusion and encephalopathy, which would include central nervous system infections, vascular problems or transient ischemic attacks, infrequently severe migraine with prolonged aura, and these considerations have to be brought forward when evaluating a patient with ADEM.

[00:05:05] So, here are some pictures of children that I've looked after who have ADEM. You can see on the panel A that this patient, this was an eight-year-old girl who was fine in the morning over the course of the day developed headache, sleepiness, went to bed that night having been very clearly lethargic and not herself, and the following morning, her mother was unable to awaken her. She was in a profound coma, and she had these multifocal areas of T2 hyperintensity. You can see that they also involve the corpus callosum in the middle of the image. And in panel B, this is her scan after a course of cortical steroids, which returned essentially to normal.

[00:05:52] In C is a different child with a slightly more flame-like appearance to the large areas of T2 hyperintensity. In D, and I hope this project for you, there's a longitudinally extensive T2 bright spinal cord in a patient with ADEM. And in E, you can see very bright areas of abnormality in the thalami bilaterally highlighting the deep gray involvement in many patients.

[00:06:18] So, one of the things that my group and I did many years ago was to compare the distribution of T2 bright lesions in the brain of patients, children, with ADEM compared to children with multiple sclerosis. And what you see here is that the distribution and pattern of lesions is remarkably similar. Qualitatively, the lesions look quite different. So, the ADEM lesions tend to be larger, less well-defined, not the rounded focal characteristic lesions of multiple sclerosis, but if you just actually quantify where the lesions are located, you can appreciate that they're not vastly different, which highlights the importance of the clinical examination to confirm the diagnosis of ADEM.

[00:07:04] In the study that I was referring to, we did note that if you had periventricular lesions, persistent black holes, and did not have this very diffuse fluffy white matter appearance, you were very likely to have multiple sclerosis and much less likely to be manifesting with monophasic ADEM. We also looked at this in a prospective Canadian study of children, all of whom were enrolled at the time of an incident demyelinating

attack. This was all comers, any child with one of those presentations I showed you on the initial slide. And what we learned was if the patient presented with optic neuritis or spinal cord involvement, so not ADEM, not encephalopathic, and did not have any brain lesions on MRI, they were very unlikely to be manifesting with multiple sclerosis and they did not meet criteria for ADEM.

[00:07:55] If they have lesions on the brain and they were younger, a high percentage of them had ADEM, almost half, and the likelihood that those children with an ADEM first attack would go on to have multiple non-ADEM events followed closely over now almost 15 years was about 3%. So, ADEM is extremely rarely the first attack of multiple sclerosis as I mentioned.

[00:08:23] This is an illustration of a child, a nine-year-old girl who came in with a 14-day history of a viral type illness, which is a common preceding experience for patients with ADEM. She became encephalopathic, she was ataxic, she was expressing double vision. She had right-sided weakness. And what you can see on the MRI is as in the other patients, slightly asymmetric, bilateral, multifocal white matter, and deep gray matter changes, including the thalamus, and then complete resolution of her imaging changes on subsequent imaging and she has had no further clinical attacks. So, the remarkable recovery on MRI, which can occur quite quickly even within the span of one to two weeks after steroids, reminds us that T2 bright signal is illustrative of water, and it may not be demyelinating entirely. It could be myelin edema because of course we don't remyelinate and repair myelin within a week.

[00:09:30] So, one of the things that we also did in our prospective study of children, many of whom had ADEM, several hundred, was to look at their white matter maturation over time. So, what we did here is diffusion tensor imaging, which is a technique using MRI to evaluate the degree to which a given region of tissue is structurally intact, if you will. So, if you were to do DTI in spinal fluid, you would find a fractional anisotropy, or the degree of alignment would be zero. It's free water. Molecules can go anywhere.

[00:10:08] If you image an area that is highly aligned, such as the midpoint of the corpus callosum where fibers are traversing in a very structured way, the fractional anisotropy is about 0.55 or 0.6. Very few things in the body are perfectly aligned with every molecule in the same direction. But as we mature, our white matter becomes more aligned. Our networks are more structurally articulated, and the normal trajectory of healthy children shown in green is for the fractional anisotropy to increase over time. And you can see that between ages five and 20. What you also see on this graph, and I'm only going to talk about the panel A, which is fractional anisotropy for the point of this discussion, is that you can see that in patients in yellow, with ADEM, instead of their white matter maturing normally and becoming more structurally intact as they mature in age, their white matter actually became less well-organized subsequent to their ADEM episodes, which occurred between five and 10.

[00:11:12] This indicates that while they may look better clinically and their bright areas of T2 signal abnormality may resolve, there is a negative impact of an event of ADEM on the subsequent maturational structural integrity of white matter.

[00:11:31] The next thing I want to talk about is what is the cause of ADEM? Well, we don't know, we do have many viral infections that have been associated with ADEM. No single virus is uniformly linked to ADEM, but many viruses have been. So, children who have experienced acute Epstein-Barr virus can develop an ADEM episode. We saw some children who had a very recent COVID infection develop an ADEM-like illness or an ADEM illness immediately thereafter. And certainly, other common viruses have been implicated. In many children, no single virus can be isolated, although they often have a recent sort of cough, cold, or sniffle in the weeks leading before they presented with ADEM. But what is more recently recognized is that a sizable number of children with ADEM have antibodies to myelin oligodendrocyte glycoprotein or MOG.

[00:12:24] In this graph, you can see the age of onset of patients with MOG antibodies, and in the far-left graph here, the light purple peak is the ADEM group, which is very heavily skewed to the younger populations, although you can also see that this can be a population that can be even over age 60 with MOG-related ADEM. The vast majority present prior to the age of 20 and even more present prior to the age of 12. So, MOG is a protein that sits on the outer lamella of myelin. So, it's very visible to the immune system and the brain. Even though it's a very minor proportion of the proteins expressed in myelin, it's a 0.05%, it is obviously important and can be targeted.

[00:13:17] So, in this image here, this is that same prospective Canadian cohort that I've been discussing. These were blood samples obtained at onset, largely untreated, in children who had presented with the first demyelinating attack. And we started this study in 2004. At that time, testing for MOG was not possible because we didn't have any of the assays to do that testing for MOG antibodies. So, these patients contributed biological samples that have been stored and they were obtained at baseline 36, 12 months and annually with some of our patients being well over 15 years now of observational follow-up. And we went back to those stored samples to look to see if patients had MOG antibodies or not. And we did this in collaboration with Patty Waters Lab in the UK.

[00:14:07] So, all samples were tested in a high-quality research environment, patched with all of the appropriate rigor that is required of looking for antibodies in this way. So, what we found is that one third of patients under age 18 presenting with the first attack of demyelination actually have MOG antibodies. So, it's not, excuse me, a rare association. And when you look at children aged under 11, almost half have MOG antibodies compared to only 15% of children aged 11 years and older. And put differently, 77% of the patients with MOG antibodies were under age 11. And you can see how young these children were.

[00:14:56] When you look at the persistence of antibodies, a few very important points because we had these serial samples, these patients were not treated as if they had MOG antibodies and we don't normally treat children unless they relapse anyway. But these samples were of course unaware of whether or not they had MOG because we didn't have the ability to test at the time. So, the first point was if you were negative for MOG antibodies when you first presented, you essentially never developed them. So, that means that if you don't have it at the beginning, it's not a late phenomenon to develop MOG antibodies, at least not in our cohort. If you had MOG antibodies at presentation, a third of the patients had persistent MOG antibodies over a prolonged period of time. 60% approximately became MOG negative over time and then 7% went up and down a bit. And in purple is the ADEM group. So, here you can see patients with ADEM and the likelihood that they've become MOG negative, and you can see that very rapidly, patients with ADEM-associated MOG IgG antibodies become MOG negative with over 80% being negative around two years from their first event.

[00:16:11] So, MOG antibodies are common in children with ADEM, but they disappear relatively quickly over time. And I forgot to mention that of the patients that have MOG antibodies under age 11, 50% of those children have ADEM. So, if you have ADEM under the age of 11, the pretest probability that you will have MOG antibodies is about 52%. So, there's also other ways that ADEM can manifest. And here we see these are lesions that are very commonly seen in patients who also have MOG antibodies, and these are bright lesions in the cortex best visualized using fluid-attenuated sequences or FLAIR. And some of these areas of FLAIR hyperintensity will also enhance. These patients tend to present with encephalopathy and seizures, sometimes with very aggressive seizures, status epilepticus that can be quite challenging to control until you treat with high dose cortical steroids and treat the MOG component, if you will. So, we and many other centers have started testing for MOG in patients that present with what we think is actually acute encephalitis, so actual brain inflammation in the cortex, or in patients who present with catastrophic nuance that status epilepticus.
[00:17:34] And here's a patient of mine that we recently managed. This is a seven-year-old boy who presented with acute encephalopathy, multiple neurological deficits meeting the criteria for ADEM, who you can see has

multiple areas actually of diffusion restriction as well as cerebral edema. This child was critically ill, required intensive care management, required placement of a CSF monitor due to his cerebral high pressures, and fortunately, with high dose steroids, plasma exchange, and a medicine called atezolizumab, he has recovered almost fully. But he very nearly succumbed from this illness.

[00:18:22] So, one of the things we think about when we see a patient with ADEM is making sure we also consider other diagnoses. So, here I have shown a patient with neuropathy, ataxia, and retinitis pigmentosa, which is a mitochondrial disease, in the middle panel, and I do have patients with mitochondrial disease, proven genetic mitochondrial disorders, who have had episodes that look like ADEM during the course of their illness. So, viral triggered encephalopathy with areas of brain inflammation. And we recognize there's quite a literature now on the overlap in some patients between mitochondrial disease and inflammatory diseases like ADEM. But here you can see that the distribution of lesions in deep gray nuclei in patients with ADEM can look a little bit like patients with mitochondrial disease, although not quite asymmetric, and can look a little bit like this patient here with mycoplasma infection who had clear evidence of mycoplasma both serologically converting as well as in the CSF.

[00:19:23] And just like everything in medicine, things can continue to get more complicated. So, this is an image of a patient story where a child has presented with a viral-triggered ADEM event who has a mutation in a nuclear pore protein called RANBP2 which predisposes to this severe form of ADEM which is called acute necrotizing encephalopathy, particularly triggered by, in this case, influenza. And patients with this condition have life-threatening deterioration in the context of viral-triggered ADEM.

[00:19:59] So, I'm going to skip this slide in the interest of time other than to point out that when we see a patient with ADEM, we typically now look for both infectious causes, as I mentioned, and we screen now for MOG antibodies. The yield is considerably lower in testing for aquaporin-4, but occasional patients will be positive. So, to end, ADEM is a clinical syndrome with multiple causes. Encephalopathy is a required feature. You should not make the diagnosis of ADEM solely on the basis of an MRI. If a child is not encephalopathic, if they do not have polyfocal clinical deficits, an MRI with multifocal white matter lesions should not be sufficient to convey the diagnosis of ADEM. 50% of children under age 11 will have serum MOG antibodies, making this a reasonable test to look for in this population. The majority of children with ADEM have a monophase of course, and even those with MOG IgG, the majority will have one attack only. So, the presence of MOG IgG does not at onset necessitate chronic immune modulation.

[00:21:06] The international consensus criteria and treatment for MOG IgG do not advocate treating with chronic immune therapy unless the patient declares themselves relapsing. I didn't have time to talk about the fact that some children with ADEM and MOG antibodies can then develop antibodies against the NMDA receptor and then manifest with NMDA receptor encephalitis, which typically has more psychiatric manifestations, although they can be encephalopathic, movement disorder, facial twitching, seizures, and these patients need to be recognized as having this dual antibody presentation.

[00:21:44] Overall, despite all of these associations, most patients with ADEM do well. They recover well from their events. And while there is a literature showing a very slight impact on cognition, the majority of patients with ADEM do not have residual cognitive impairment of any substantial amount, although young children post-ADEM can be a bit socially disinhibited and a little bit more difficulty with attention and focus. And many parents tell me that is a sequela of ADEM in their child. So, I hope this has been helpful. If there are questions, do not hesitate to reach out to me. And I thank everyone for their kind attention.